Assessment of spontaneous motor behaviour in relation to umbilical artery pH in full-term infants : a method to predict neurodevelopment?

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a method to predict neurodevelopment?

Marijtje van Hall

ASSESSMENT OF SPONTANEOUS MOTOR BEHAVIOUR IN RELATION TO UMBILICAL ARTERY pH IN FULL-TERM INFANTS

a method to predict neurodevelopment?

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. A.C. Nieuwenhuijzen Kruseman,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 9 april 1999 om 14.00 uur

door

MARIA HENRIETTE JOHANNA ANNA VAN HALL

geboren te Eijsden op 24 juni 1964

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The proper study of mankind is man

(POPE, ESSAY ON MAN 2, 2)

Onze doden horen tot de onzichtbaren, maar niet tot de afwezigen
H. PAUS JOHANNES XXIII

Voor papa, mama en Jos

Woord vooraf

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'DE TIJD OM TE DRINKEN EN MET LOSSE VOET DE GROND TE RAKEN, BREEKT AAN'.
(naar Horatius, Carmina 1, 37, 1-2)

Marjolette

Contents

List of abbreviations

- ATP *adenosine triphosphate*

- Ca^{2+} *calcium ion*
- COPD *chronic obstructive pulmonary disease*
- CT *computed tomography*

- DNA *deoxyribonucleic acid*

- e.g. *exempli gratia*
- EMG *electromyogram*

- GM code *general movement code*

- HELLP *haemolysis, elevated liver function tests, low platelet counts*

- i.e. *id est*
- interm. *intermediate*

- MDI *mental developmental index*

- Na^+/K^+ *sodium/potassium*
- n.e. *neurological examination*
- n *number*
- NMDA *n-methyl-d-aspartate*
- NMR *nuclear magnetic resonance*

- pCO_2 *pressure of carbon dioxide*
- PDI *psychomotor developmental index*
- PET *positron emission tomography*
- pma *postmenstrual age*
- PMN *polymorphonuclear*
- pO_2 *pressure of oxygen*

- SD *standard deviation*
- SPECT *single photon emission computed tomography*

- 1st *first*
- 2nd *second*
- 3rd *third*

Chapter 1

General introduction

Infants suffering adverse perinatal conditions may be at risk of disabilities in later life. The detection of neurological signs shortly after birth in these infants may predict the quality of their neurodevelopment. One of such adverse perinatal conditions is birth asphyxia: a condition of hypoxia-ischaemia in the neonate. The degree of hypoxia-ischaemia in the neonate can objectively be assessed by the degree of acidemia in fetal blood. However, it is unknown whether and to what extent the degree of fetal acidosis is related to the degree of fetal brain lesion. Therefore, it remains unclear whether (the degree of) fetal acidosis, as measured from umbilical artery pH, can be reliably used to predict brain lesion.
Various methods such as neurological examinations, developmental scales, cranial ultrasound, CT, NMR, electroencephalogram, evoked potentials, doppler-velocimetry, PET and SPECT-scan are used to assess (the extent of) hypoxic-ischaemic brain lesion. All these methods provide information on the central nervous system state of the infant. However, since they also have shortcomings, there is still room for improved clinical tools to assess the degree of neurological damage due to birth asphyxia.
The qualitative assessment of spontaneous motor behaviour[14,21-25,28-30,35,36,44-49,58,67-69,100-105,132] is a promising method to evaluate brain function, and can be performed without interference or manipulation of the newborn. Whether and to what extent the degree of fetal acidosis, defined by umbilical artery pH, affects the quality of motor behaviour is still unanswered.
This thesis considers the usefulness of studying the quality of spontaneous movement types throughout a period of time in relation to subsequent neurodevelopment in 85 full-term infants within a wide range of umbilical artery pH.

conclusion: it is unknown whether and to what degree fetal acidosis, as measured from umbilical artery pH, affects brain function. A promising method to measure brain function clinically is the qualitative assessment of spontaneous motor behaviour. This thesis considers whether studying the quality of spontaneous movement types throughout a period of time in relation to subsequent neurodevelopment in full-term infants within a wide range of umbilical artery pH is useful. ■

CHAPTER 2

INTRODUCTION

BIRTH ASPHYXIA: A DEFINITION

'Asphyxia' is etymologically derived from a Greek word meaning pulseless, which in this thesis refers to a condition of hypoxia-ischaemia in the neonate. Up until the present, the definition of birth asphyxia is a controversial issue. Although the degree of asphyxia can be measured in blood, its neurodevelopmental consequences are difficult to evaluate. Indirect indicators of asphyxia such as fetal heart rate abnormalities, meconium staining of the amniotic fluid, delayed start of breathing, low Apgar score and early onset of abnormal neurological behaviour are frequently used as indicators. Some authors have proposed a combination of fetal pH, Apgar score and signs of cerebral dysfunction to define birth asphyxia.[39]

Apgar score. The Apgar scoring system assesses the neonatal condition at 1 and 5 minutes after birth by scoring the items heart-rate, respiration, muscle tone, reflexes and skin colour, each varying from 0 to 2. Both the American College of Obstetricians and Gynaecologists and the American Academy of Pediatrics[1,2] have challenged the use of the Apgar score as the sole indicator of the degree of birth asphyxia since there are several other factors that may account for a low Apgar score besides asphyxia such as gestational age, maternal medications and type of anaesthetic administered. Furthermore, there is a wide interindividual variability when assigning Apgar score values.

Sykes[119] found that only approximately 20% of the neonates with a 1 and 5 minutes Apgar score below 7 had an umbilical artery pH ≤7.10 (base deficit ≤-13 mmol/l). The Apgar score did not reliably reflect the degree of acidosis at delivery, as measured from umbilical artery pH.[24,129]

Neurological symptoms. Abnormal neurological signs are another frequently used indicator of asphyxia. When several of such signs are present, the syndrome is called hypoxic-ischaemic encephalopathy. These signs include impaired consciousness and brain stem dysfunction as well as seizures, low tone and loss of primitive reflexes. According to Sarnat and Sarnat,[112] the postnatal clinical course of an infant (together with EEG changes) reflects the severity of the hypoxic-ischaemic insult. However, none of the clinical (or electroencephalographical) characteristics are specific to postanoxic encephalopathy.[4,5,9,13,112] In addition, Hull and Dodd reported on a group of neonates with similar encephalopathies, showing no indication of birth asphyxia.[59]

Fetal pH. The degree of asphyxia can be reliably defined by the degree of acidemia, hypoxemia, hypercapnia and base deficit. Reduced placental perfusion not only leads to hypoxia but also impairs the release of carbon dioxide from the fetus, resulting in respiratory acidosis. Anaerobic glycolysis leads to a gradual accumulation of pyruvate and lactate and to the development of metabolic acidosis. Intra-uterine asphyxia results in a mixed metabolic-respiratory acidosis. Although birth asphyxia may be reflected in fetal acidosis, defining a certain pH cut off point to separate asphyctic from non-asphyctic infants remains arbitrary. Statistically, a pH ≤2 SD below the mean for a population could be a possible definition for acidosis. One study considered an umbilical arterial pH ≤7.10 as a reasonable cut off point.[122] Other studies state that normal umbilical artery pH varies from ≥7.18 to ≥7.00.[25,34,41,70,109,139] Other investigators consider umbilical arterial base deficit as a marker of asphyxia,[79,114] and yet others suggest that arterial pH after the first hour of life might be a better marker to define asphyxia than umbilical artery pH.[11]
Defining fetal asphyxia by means of the degree of acidosis has several limitations:

1. Acid base studies from umbilical artery pH cannot distinguish between fetal acidosis due to primary fetal pathological conditions and that due to maternal acid-base disorders.[107] However, in current obstetric practice, significant maternal acidosis resulting from physical exertion of labour, exacerbated by dehydration, infection, or hypoglycaemia and caused by inborn metabolic errors[54,118] or alkalosis (secondary to hyperventilation) is unusual but if present, can be detected. In such cases, the added value of base deficit helps to differentiate the fetal from the maternal problem.[107]
2. Umbilical artery pH does not reflect asphyxia if it occurred remote from delivery.[107]
3. Acidosis at delivery reflects the cumulative events of labour. The severity of metabolic acidosis can be defined, but there is no indication of its duration.[74,79] However, pH measurements of the umbilical artery blood objectively reflect the presence and severity of fetal acidosis, and fetal hypoxia is the most likely cause in the absence of other potential causes. Therefore, umbilical artery pH remains the most reliable indicator of birth asphyxia. *Statistically,* a pH ≤7.10 could be considered abnormal, but whether this reflects a *biological* abnormality has been insufficiently studied.

In conclusion: although blood gases do not reflect the duration of fetal acidosis, it is the only objective indicator of hypoxia-ischaemia in the neonate. However, it is unknown whether and to what extent the degree of fetal acidosis, as measured from umbilical artery pH, is related to the degree of fetal brain lesion. *In addition,* there is no consensus on how the degree of hypoxic fetal brain lesion should be clinically evaluated. The predictive value of a low pH at birth on later development remains a debatable issue.

The next paragraph describes the effects of hypoxia at cellular level, with reference to current ideas on the processes that lead to neuronal cell death.

Pathophysiology of cerebral hypoxia-ischaemia

In brain hypoxia, there is a reduction in oxygen supply and in ischaemia, there is a depletion of both oxygen and energy substrates to the brain, resulting in a cascade of events that eventually could lead to cell death. One of the first consequences of hypoxia-ischaemia is a shift from oxidative to anaerobic metabolism with the production of metabolic acids leading to intracellular and extracellular acidosis. Anaerobic glycolysis alone cannot supply the required energy and is only a short-term rescue mechanism.
Lack of oxygen results in energy failure. As energy supply fails, cellular depolarization occurs. An important system involved in the initiation of ultimate cellular breakdown relates to the activation of certain receptors. Under normal conditions, these receptors are activated by amino acids that act as neurotransmitters, glutamate being the most important one. The activation of these receptors leads to the opening of ion channels through which cations, mainly Ca^{2+}, can pass independently of an electrochemical (voltage) gradient across the plasma membrane.[117] Oxygen shortage depolarizes neuronal membranes, causing the release of glutamate. Glutamate activates the voltage dependent N-methyl-D-aspartate NMDA receptors, allowing a massive influx of calcium into the cell.[31] Another effect of the activation of NMDA and non-NMDA receptors by glutamate is an eventual increased synthesis in nitric oxide by neurons.[32]
In addition to the receptor dependent cation influxes, voltage dependent influxes also play a role: a depletion of energy leads to ion pump failure by impaired ATP dependent Na^+/K^+ transport. The ensuing cellular depolarization results in an increased membrane permeability to cations, leading to an intracellular accumulation of calcium and sodium, accompanied by movement of water into the cell, leading to cellular edema. This early intracellular cytotoxic edema is thought to make capillaries collapse and thus impede (re)perfusion. Several hours after the primary insult, vasogenic edema occurs as a result of the increased permeability in the capillaries, leading to an accumulation of fluid within the extracellular space. Consequently, there is an increase in intracranial pressure that reaches its maximum 36 to 72 hours after a severe hypoxic-ischaemic insult in the neonate.[82] Intracranial pressure can increase to the point of further impairing cerebral blood flow.

The above described cellular calcium overload activates several proteolytic enzyme systems, ultimately resulting in cell breakdown.
Besides the cation-ion influx related damage, there is another mechanism that adds to cellular dysfunction. During normal oxidative processes, a small proportion of oxygen is converted into the free radicals superoxide ion, hydrogen peroxide and the highly reactive hydroxyl radical. Defence mechanisms against oxygen-derived free radicals are present in the form of endogenous scavengers. In the case of hypoxia-ischaemia, oxygen-derived free radicals accumulate. Rapid catabolisation of energy rich nucleotides (DNA-damage) during asphyxia results in the accumulation of hypoxanthine and xanthine. When oxygen is added to a system rich in hypoxanthine and xanthine, oxygen-derived free radicals are formed in large quantities, provided that the enzyme xanthine-oxidase is available.[121] Xanthine-oxidase can be formed in the endothelium of brain capillaries,[12] and its production is induced by both oxygen shortage and increased intracellular calcium concentrations.[85]
Calcium overload not only activates xanthine-oxidase, leading to massive free radical production, but also phospholipase, which facilitates the production of arachidonic acid out of membrane phospholipids (membrane-damage). Arachidonic acid is the precursor of thromboxane A_2 and prostacyclin. These substances have opposite functions, vasoconstriction or vasodilation, and platelet aggregation or inhibition of aggregation respectively. Normally, the production of these compounds is adequately balanced. During lack of oxygen, however, prostacyclin synthesis is inhibited and thromboxane A_2 synthesis increases, stimulating vasoconstriction and platelet aggregation, which add to the extension of an ischaemic area.

Especially during reperfusion, an elevated arterial oxygen content leads to the formation of large quantities of oxygen-derived free radicals from hypoxanthine and xanthine by xanthine-oxidase. In the presence of free iron in the cerebral spinal fluid, a highly reactive hydroxyl radical, is formed. Moreover, during reoxygenation by reperfusion, the resulting vasodilatation facilitates the distribution of the locally accumulated thromboxane A_2 over a larger cerebral area, threatening potential viable tissue, the penumbral zone.[126] Furthermore, the accumulated arachidonic acid serves as a substrate for two different oxidative enzymatic pathways: the lipo-oxygenase and cyclo-oxygenase pathways. Lipo-oxygenase pathways metabolize arachidonic acid to the leukotriene system, effectively contributing to the generation of more oxygen-derived free radicals.[70] These radicals tend to perpetuate a chain reaction since they accelerate the

formation of arachidonic acid via phospholipid degeneration and lipid peroxidation. On the other hand, cyclo-oxygenase pathways contribute to the formation of a host of prostaglandins. The net vascular effect of prostaglandin formation in the brain is vasoconstriction since the postasphyxial brain has a limited capacity to synthesize the vasodilatator prostacyclin,[106] whereas the production rate of the potent vasoconstrictor thromboxane A_2 is high.[37] This disbalance probably results in a secondary vasoconstriction that could extend to the penumbra. In large cerebral vessels, endothelium-dependent relaxation is enhanced in two different ways: the action of prostacyclin and nitric oxide. Endothelial cell damage, initiated by oxygen-derived free radicals, leads to a polymorphonuclear (PMN) leukocyte adherence with an increased tendency to vasoconstriction and reduced vasodilatation that could extend to the penumbral regions.[51] Normally, nitric oxide synthetase converts arginine into nitric oxide. In ischaemia, there is a lack of arginine, but during reperfusion and reoxygenation, unregulated overproduction of nitric oxide may result in the production of oxygen-derived free radicals, which are cytotoxic. Because of reperfusion following hypoxia-ischaemia, there can be a perpetual chain reaction of free radical production of hypoxanthine/xanthine, arachidonic acid and nitric oxide, a production of vasoconstrictors by arachidonic acid along with the occurrence of polymorphonuclear leukocyte interactions with the endothelium, impairing reperfusion.

Another mechanism that causes cellular death is apoptosis. Apoptosis, or programmed cell death, occurs in neurons that fail to make connections to trophic support. During asphyxia, normally suppressed programmed cell death may be activated and continue activated for a long time after the insult.[84,86] However, it is important to note that not all authors accept a clear distinction between apoptosis and immediate necrosis initiated by intracellular calcium influxes.[33,81]

Thus, factors influencing or mediating cell death depend on the level and duration of ischaemia and on whether there is tissue reperfusion. High levels of intracellular calcium mediate a number of different events in the cascade of cellular breakdown. Reoxygenation following asphyxia or reperfusion following ischaemia cause a surge of free radical production, vasoconstriction and furthermore, an inflammatory response, all of which may add to the possibility of neurons and supportive cells ultimately dying.[140] The information currently available demonstrates that the response of the brain to an ischaemic insult is highly complex, remaining incompletely understood. Considering the complexity of processes that ultimately lead to

neuronal cell death, the sole measuring of umbilical artery pH might not reliably reflect the ultimate overall consequences of these processes.

Although brain damage due to hypoxia may be diffuse, particular vulnerability of some neuronal populations may result in selective neuronal cell death.[125] The type of acute lesion, and final effect on the brain, depend on the stage of development at the time the lesion was inflicted.[38,82] Lesions are usually mixed. However, white matter infarction predominates in preterm infants, while cortical damage predominates in full-term infants. White matter infarction or periventricular leukomalacia disrupts the myelinated fibres descending from the cortical pyramidal and projecting on the spinal motor neurons that supply not only leg muscles (resulting in diplegia) but also arm and hand muscles.[72] In full-term infants, the parasagittal parietal cortex is particularly susceptible to hypoxic-ischaemic lesion.[130] These cortical regions correspond to the border zones (also called watershed areas) of circulation between the anterior and middle cerebral arteries and the middle and posterior cerebral arteries. Often, laminar necrosis of the deeper layers of these parasagittal cortex region is seen. Again, this focal loss of cells is thought to be the result of cortical hypoperfusion. The layers of cell loss correspond to the terminal regions of the short penetrating arteries that originate at right angles from the larger vessels in the overlying pia.[135] However, the concept of watershed regions has been questioned.[80] Hypoxic-ischaemic lesions comprise cortical necrosis with involvement of the immediately subjacent white matter in a characteristic distribution, encompassing the parasagittal, superomedial areas of the convexities bilaterally with posterior (parieto-occipital) regions more involved than anterior ones.[130] Clinically, this is represented in proximal spastic quadri paresis involving arms more than legs.[131] More selective neuronal necrosis in full-term infants has been found in the colliculi, hippocampus, reticular formation, cranial nerve nuclei, dentate nucleus and substantia nigra.[71,128] Severe hypoxia-ischaemia can also produce lesions in the thalamus and basal ganglia.[27,128] During development, there may be a selective vulnerability of certain neurons, i.e., those predominantly innervated by glutaminergic neurons. It is tempting to assume that such cells are vulnerable because they are densely occupied by calcium channels, mediating strong calcium accumulation.[96] Particular vulnerability of some neuronal populations may result in a selective neuronal necrosis, consequently reflected in certain clinical signs. There are vulnerable regions related to hypoxic-ischaemic lesions in the neonatal brain which are partially age-dependent such as parasagittal parietal cortex, basal ganglia and thalamus in full-term infants. The exact

reasons for this particular vulnerability is not fully understood. Clinical features are likely to be related to the extension and degree of cerebral damage, being not only related to postmenstrual age but also to certain aspects of development.

Compared with the adult brain, the neonatal brain is relatively resistant to hypoxic-ischaemic lesions. This resistance is thought to reflect a lower metabolic rate as a consequence of smaller and less branched neurons with fewer synapses.[53] Another known factor is that there is a marked induction of neurotrophic factors such as transforming growth factor beta 1 and insulin-like growth factor 1. Transforming growth factor can suppress the cytotoxic activity of inflammatory cells. Insulin-like growth factor is known to be highly neurotrophic and might reduce apoptosis.

In summary:

hypoxia-ischaemia of the brain tissue leads to a cellular calcium overload and edema. Calcium perpetuates a chain reaction of oxygen-derived free radical production, which is cytotoxic. Calcium and free radicals cause vasoconstriction. Reperfusion following hypoxia-ischaemia leads to the formation of oxygen-derived free radicals, extended vasoconstriction and inflammatory toxicity. At the same time, apoptosis is activated. Hypoxic-ischaemic brain damage is diffuse in vulnerable areas, especially parasagittal parietal cortex, basal ganglia and thalamus, which could explain some of the clinical signs and symptoms seen in neonates that have experienced birth asphyxia. Currently, many drugs that are being developed and tested could ameliorate the consequences of brain ischaemia or hypoxia and if proven effective in certain clinical domains, they may eventually be tested to improve the neurological outcome of neonates that suffered birth asphyxia.

Relationship between neonatal asphyxia and neurological outcome

Several studies that examined the neurological outcome of asphyctic neonates defined asphyxia considering different umbilical artery pH or base deficit.[25,26,34,41,52,70,74,76,77,109,136]
The umbilical artery pH cut off point below which acidosis was defined varied from 7.16 to 7.00.[25,26,34,41,70,109,136]
In one study on full-term and preterm neonates, the sensitivity and positive predictive value of pH <7.16 on adverse neurological outcome at one year of age were 21% and 8% respectively.[109] When the umbilical

artery base deficit was below -12 mmol/l, the number of children with neurological deficits increased at one year of age, with an additional increase when base deficit increased.[74,77] This study defined asphyxia biochemically by umbilical artery base deficit, not by pH levels. Several studies found that the frequency of early neonatal sequelae related to intrapartum asphyxia rose with increasing degree of acidemia in the pH group below 7.00.[26,41,136] Some authors have suggested that brain damage may occur beyond a critical threshold of fetal asphyxia, but the level of such threshold remains unclear.[74,77]
Although the degree of metabolic acidosis is probably the most reliable reflector of the degree of neonatal asphyxia, it yields no information on the duration of such asphyxia. Nature, degree, duration of intrapartum asphyxia as well as blood gases after the first hour may influence the degree of ultimate neurological abnormalities.[11,79] It is clear that severe asphyxia may result in severe neurological sequelae, but the way in which the degree and duration of hypoxia combine in a particular human fetus to determine an ultimate central nervous system lesion remains unclear.

Differences between study populations is an important variable when determining the comparability of studies on asphyxia at birth and neurological morbidity. Several factors other than asphyxia may cause neurological deficits and must be taken into account. Dyxhoorn et al. compared a low-risk population with a population with a similar distribution of pH values and birth weights, but with one or more complications during pregnancy and delivery such as second stage labour longer than 60 minutes, no spontaneous delivery, no vertex position at delivery and congenital malformations.[26] The low-risk population had a frequency of early neonatal neurological abnormalities that was less than half that in the total group.[26] Low et al. studied the association between intrapartum fetal asphyxia, determined biochemically by a base deficit value below -12 mmol/l, and long-term neurological outcome in 2 study groups.[76,77] In full-term neonates, appropriate for gestational age, no neurological handicap or delay in development was found at 1 to 6 years of age neither in the asphyctic nor in the control group.[76] However, in the full-term neonate study group, including those with growth retardation and those with severe respiratory complications requiring mechanical ventilation, Low et al. found a higher rate of neurological deficits in the asphyctic than in the control group.[77] Children with neurological deficits showed fetal growth retardation and severe respiratory complications shortly after birth more often.[77] Others have suggested that the frequency of ultimate sequelae of asphyxial insults in preterm neonates may be higher than that in full-term infants.[109] Factors such as growth retardation,

prematurity and respiratory problems in neonates may, therefore, influence the impact of an asphyxial insult on ultimate neurological morbidity. The variability in neonatal morbidity between the above described studies obscures the relationship between neonatal asphyxia and outcome.

A proper appreciation of the clinical significance of intrapartum asphyxia should yield reliable outcome measures. The Newborn Behavioural Brazelton Assessment Scale, which measures the degree in which a neonate is able to achieve, maintain, and modulate state control during both sleep and alert periods after sensory stimulation, is thought to reflect the maturity and integrity of the high order central nervous system control[18] and may identify minimal central nervous system dysfunctions. Using this scale 3 days after delivery, Low found no significant differences between an asphyctic (base deficit below -12 mmol/l) and a control group.[78] However, 2 weeks after delivery, the asphyctic group scored significantly lower.[78] Others have examined full-term neonates on the fourth or fifth postnatal day by quantifying the neurological findings according to the 'neurological optimality concept', as described by Prechtl.[79] This concept defines the optimal range for 60 representative neurological items, resulting in a neonatal neurological optimality score. Only neonates born with umbilical artery pH <7.00 showed a small increase in minor neurological signs in the neonatal period.[26] Both the behavioural Brazelton scale and Prechtl's neurological optimality score are methods that allow a detailed assessment of the neurological condition in the newborn, but so far, they have only been used to evaluate short-term outcome. And yet, minor abnormal newborn behaviour due to a central nervous system hypoxic-ischaemic insult may become evident later, in the first weeks of life.[78] Furthermore, minor neonatal neurological symptoms may improve as time passes.[26] Therefore, late clinical manifestations of subtle damage in the central nervous system may go undetected by the Brazelton or Prechtl assessment.
The usual methods to assess neurological condition in children during later development are (repetitive) clinical neurological examinations and a variety of standardised neurodevelopmental tests related to motor, cognitive, language, memory functions and school performance. Neurodevelopmental assessments of motor and cognitive functions in a child become more accurate as it grows older. However, language, memory and school performance cannot be tested in the first 1.5 years of age. Few investigators have studied the relationship between fetal asphyxia and long-term neurological outcome using neurological examinations, standardised developmental tests or both.[25,34,41,52,70,76,77,109] These studies found only a weak or no correlation between birth asphyxia and long-term neurological outcome. No motor, cognitive, or language deficits were

identified by diverse standardised neurodevelopmental tests between 1 and 6 years of age in born at term, appropriate for gestational age asphyctic children.[76] Also, no differences in motor, cognitive development or serial tests of memory were reported in ages 4 to 8 years between asphyctic full-term newborn infants and their matched controls.[32] Besides, no statistically significant associations between asphyxia at birth and neurological outcome at 4.5 years of age, as determined by developmental tests, were found.[25] Except for the neonatal period, there were no data on the first year of life in these studies. Several studies had flawed study-designs: follow-up was limited to neonates with an abnormal neonatal neurological examination,[34,41] duration of follow-up varied[41,72] or was incomplete.[34,129] The duration of follow-up in the various studies varied from 6 months to 8 years of age. Despite the shortcomings of their studies, some researchers concluded that newborn infants with hypoxic-ischaemic encephalopathy have an increased risk of future deficits.[32,76,77] Because of the various differences in study design, results of the above mentioned studies are difficult to compare. Moreover, the absence of unique standardised outcome measures leaves the question of the relationship between neonatal asphyxia and risk of future functional deficit largely unanswered. For a reliable assessment of this relationship, study groups should be constituted by full-term low-risk neonates, and detailed neurological examinations in combination with standardised neurodevelopmental tests should be performed at different follow-up periods, as was done in this thesis.

In conclusion: whether (the degree of) fetal acidosis at delivery can be used as a reliable predictor for long-term neurological outcome remains insufficiently validated.

Quality of spontaneous movement to asses brain function

There are several methods to study brain function in newborn infants. One method is the neurological examination based on reflexes,[6,98] which unfortunately involves manipulation of the newborn. It remains highly questionable whether this method can lead to an appropriate evaluation of all relevant functions of the nervous system. The study of spontaneous motor behaviour such as sucking,[137,138] eye movements,[50] facial movements,[93] early reaching[55,56] and leg movements[120] can be performed without manipulation of the neonate and is probably a more valuable method[137,138] since spontaneous motor behaviour may be regarded as complex manifestations of mechanisms involving the nervous system.

Quantitative and qualitative aspects of spontaneous motor behaviour can be distinguished. As the quality of spontaneous movement not only reflects the presence of movements but also the maturity and integrity of the brain, the quality of spontaneous movement is most suitable to detect slight brain dysfunctions. The most appropriate way to assess the quality of spontaneous motor behaviour is the observation of general movements,[105] which frequently occur in newborn infants. Therefore, the qualitative assessment of spontaneous general movements in neonates is a promising method to evaluate the integrity of the brain, and can be performed without interference or manipulation of the newborn.[29,100-103]

General movements have been defined as a series of gross movements of variable speed and amplitude, involving all parts of the body, without distinctive patterning or sequencing of body parts, lasting from a few seconds to several minutes.[100] By ultrasound, general movements have been recognized as of 8 postmenstrual weeks onwards in fetuses.[132] General movements usually disappear at about 4 months postnatal age when goal-directed movements take over.[48,58,104]

General movements in healthy full-term neonates have been described using 2 different methods.[21,48,58,68,69,104] Prechtl et al., using visual gestalt perception, defined 'writhing' general movements[58,104] first with a 'tight', later with a 'loose' appearance[48], changing into 'fidgety' general movements at about 9 weeks after birth.[48,58,104] The items used for this global assessment were: fluency, variability and complexity.[29] Van Kranen-Mastenbroek et al. studied general movements in the first postnatal week by defining 20 items that assessed the quality of general movements.[68,69] The scores of these items showed significant mutual correlation: overall speed, fluency, overall variability, and particularly variability in arms and legs separately, were used to define dominant movement types.[68,69] Three dominant movement types were classified: type 1 (characterised by a variable speed, fluent performance and variable movement), type 2 (fast, abrupt/jerky and variable), type 3 (fast speed, abrupt/jerky performance without variability in movement).[68,69] However, it is still necessary to establish a method that allows to select items and quantify the relevant movement types. Even though both Prechtl and van Kranen-Mastenbroek studied the quality of general movements in healthy full-term newborns, comparing their results is difficult because none of the 3 types of movements, as described by van Kranen-Mastenbroek et al.,[68,69] correspond completely to the definition of 'writhing' quality as given by Prechtl et al.,[21,48,58,104] who based his assessments of the quality of movement on different features.[29,68,69]

Furthermore, Prechtl et al. reported only one movement type per infant per observation session, based on 3 arbitrarily chosen general movements,[29] while van Kranen-Mastenbroek et al. reported variability within movement types per infant per observation session. Van Kranen-Mastenbroek et al.[68,69] did not study the developmental course of general movements.

Although the sensitivity of a single general movement assessment is high, assessments of the quality of general movements should be repeated at different ages because of an increasing specificity with increasing age.[29,100-103,110] In normal development, the quality of general movements changes.[22,48,58,104] In full-term infants, the developmental change from 'tight writhing' into 'fidgety' general movements was more closely related to postmenstrual than to postnatal age.[48] However, Cioni et al. reported that low risk preterm infants developed 'fidgety' general movements earlier than full-term infants.[22] According to this, during development, endogenously generated maturational processes may be influenced by extrinsic factors, complicating the definition of optimal age at which assessments should take place. Coinciding with a change in quality of general movements, other processes of postural control occur such as stabilization of head balance, performance of pelvic tilting, bringing hands to midline and hand-eye coordination.[22,48,95] Whether and which developmental processes are influenced by extra-uterine life is not fully understood.[22,48]

Whether the influence of behavioural states was taken into account when studying general movements is not clear.[47,68,69] One of the states that should be excluded from observation sessions is when the infant is crying. According to Prechtl et al., the quality of general movements is best studied in what they called behavioural state 4:[97] eyes open, continuous gross motor activity,[47] whereas according to van Kranen-Mastenbroek et al.,[68,69] differentiating between sleep and wakefulness is unnecessary.

The normal repertoire of general movements in healthy full-term newborns can be used as a reference when studying full-term newborns at risk of neurodevelopmental abnormalities. The effect of intra-uterine growth retardation[68,69] or hypoxia-ischaemia[103] on spontaneous motor behaviour has been investigated. Van Kranen-Mastenbroek et al. observed that small for gestational age newborns showed two different movement types in addition to the normal movement repertoire.[68,69] Prechtl et al.[103] found that general movements in asphyctic newborns differed clearly from those in normal newborns and attributed this

phenomenon to a decrease in neuronal functions, which play a role in normal motor behaviour. They stated that the main characteristic of general movements in asphyctic full-term newborns was a loss of variability, described as a 'poor repertoire' and 'cramped-synchronized' general movements.
In time, some brain functions can recover, but also ongoing maturation might disclose dysfunctions, expressing lesions hitherto silent. Therefore, a qualitative assessment of the development of general movements is best to predict neurological outcome. Prechtl et al.[103] stated that persistence, or disappearance, of both normal and abnormal general movements as well as type of abnormal general movements predict long-term neurological outcome. However, some aspects of their study design such as the use of various indicators of birth asphyxia need further study. All infants had a history of fetal distress (documented by signs such as fetal bradycardia, late decelerations of the fetal heart rate, meconium aspiration, cord or neonatal pH <7.10 or in combinations of the above), low Apgar score and need for resuscitation at birth. Furthermore, the method to assess general movement types[103] should be considered with caution since the overall assessment per infant was reached based on only 3 at random selected general movements per infant.

Therefore, the question of whether and to what degree fetal asphyxia affects the integrity of the brain and therefore normal motor behaviour, as seen in the quality of general movements, remains largely unanswered. Studying these relationships requires an operational definition of the quality of general movements and a clear definition of birth asphyxia. This thesis attempts to consider all these variables in order to develop a proper study design.

In general, the assessment of the quality of general movements is a method to evaluate brain function in newborns at risk of brain damage. Following fetal acidosis, the qualitative assessment of motor behaviour during development could be proposed as a method to predict neurodevelopmental outcome.

The role of cranial ultrasound in full-term asphyctic neonates

Characteristic ultrasound findings in the first postnatal week in infants with severe hypoxic-ischaemic lesion are: increased parenchymal echogenicity[116] and effacement of cortical sulci as a result of cerebral edema.
In full-term infants, cranial ultrasound sensitivity is low:[7,42,63,110,116,133] most ultrasounds performed on neonates

with hypoxic-ischaemic encephalopathy are normal. If the entire brain shows increased echogenicity because of diffuse cytotoxic edema, the relative echogenicity of the various structures of the brain remain unchanged, making detection of edema difficult.[8] After the first week of life, increased echogenicity may resolve, persist or result in cavitation by necrosis.[7] However, hypoxic-ischaemic lesion to the brain in full-term neonates often occurs in the basal ganglia, thalami, brain stem (regions that are deep within the brain and rarely cavitate) and the fronto-parietal convexity (a location difficult to visualize via the anterior fontanelle).[8,116] Because of these factors, ultrasound sensitivity at birth is low,[42,63,116,133] but higher if performed 7 days after birth.[7] Abnormal ultrasound findings accurately predict adverse neurological outcome. Its specificity is high.[7,42,112,116]

Thus, cranial ultrasound performed on asphyctic full-term infants is not a valuable method to predict neurodevelopmental outcome because of its low sensitivity.

AIMS OF THIS STUDY

- To study the quality of spontaneous motor behaviour in full-term infants within a wide range of umbilical artery pH, by a selection of movement types based on the scoring of various items of each movement (chapter 4).
- To study the influence of umbilical artery pH on the quality of spontaneous motor behaviour in full-term infants in the first months of life (chapter 5,6).
- To study the relationship between the quality of spontaneous motor behaviour in full-term infants and their neurodevelopment at 18 months of age (chapter 7).

CHAPTER 3

INFANTS AND METHODS

INFANTS

nclusion criteria

We included in the study newborns:

1. with a known umbilical artery pH;
2. with a postmenstrual age of 37-42 weeks;
3. with a birth weight of between the 2.3 and 97.7 percentile of the Kloosterman intra-uterine growth curves;[64]
4. born in vertex position;
5. after obtaining parental informed consent.

Postmenstrual age was the interval between the first day of the last menstrual period and the day of birth. When the last menstrual period was uncertain, postmenstrual age was assessed by using the available data on fetal biparietal diameter, measured by ultrasound before the 20th week of pregnancy.

xclusion criteria

We excluded from the study newborns:

1. with hypoxia-ischaemia other than caused by perinatal adverse conditions as measured from umbilical artery pH;
2. with meconium aspiration, respiratory distress and infections or born after a complicated pregnancy (table 1);[65]
3. with malformations;
4. born to women using medication (except for ferro-therapy, vitamins), alcohol or drugs during pregnancy;
5. born before 37 weeks, in breech presentation or with an inappropriate weight for gestational age.

Also, exclusion occurred during follow-up due to several pathologies.

Methods

Umbilical blood gas determination

Blood for umbilical blood gas determination was obtained in all deliveries. Arterial umbilical blood (2 ml) was drawn from a double clamped segment of the umbilical cord into a heparinized syringe. Blood gas determination was then performed on an AVL 995 analyser or a Ciba Corning 278 blood gas system within 15 minutes after collection and corrected for 37 °C. In the group of newborns with a pH below 7.10, arterial blood gases were determined at one hour after birth. Umbilical artery pH was used as selection criterion in this thesis.

Study population

Based on the 95% confidence intervals,[11] we divided the study population into 3 subgroups: a) *normal pH*; umbilical artery pH ≥7.20, b) *intermediate pH*; umbilical artery pH ≥7.10 and <7.20 and c) *low pH*; umbilical artery pH <7.10.

In the group with a pH below 7.10, serum glucose on the first day and serum calcium on the second day after birth were determined because, besides pH, abnormal glucose and calcium levels may influence motor behaviour.
These neonates also had a cranial ultrasound between the tenth and fourteenth day after birth to assess parenchymal echogenicity, effacement of cortical sulci and cavitation as indicators of hypoxic-ischaemic brain lesion. In the absence of these findings, cranial ultrasounds were classified as normal.

Neurological examination

All neonates were neurologically examined[36] between the third and eighth postnatal day. Signs considered were: head circumference, arousal, eye movements, tone regulation, asymmetry and seizures. The classification of signs assessed resulted in the categories: *normal*, *suspect* and *abnormal*. In the absence of abnormal neurological signs, the examination was considered normal. The examination was considered suspect when disturbed arousal, eye movement disorders, transient tone regulation disorders (hypotonia or hypertonia) and transient hemiparesis were observed. Abnormal neurological examinations consisted of persistent tone regulation disorder, manifest hemiparesis and/or seizures.
We also performed a neurological examination[6] on all infants at around 6 weeks, 12 weeks, 9 and 18 months of age. Neurological signs considered were: head circumference growth curves, arousal, eye movements,

tone regulation, asymmetry and development. In addition to the above mentioned neurological signs considered abnormal, deviant growth curves of head circumferences and developmental delays were also assessed. Results were divided into categories: *normal, abnormal* and *suspect*. The examination was considered normal in the absence of abnormal neurological findings. When abnormal signs persisted during serial examinations, the neurological examination was considered abnormal. When abnormal neurological signs did not persist, infants were classified as suspect.

For analysis, *suspect* and *abnormal neurological examinations were considered abnormal.*
The first 3 neurological examinations were grouped according to postmenstrual age into 37-43 weeks, 43-49 weeks and 49-55 weeks respectively.

Bayley Scales of Infant Development

Medical psychologists tested all infants using the standardised Bayley Scales of Infant Development[19] at 9 and 18 months of age. The Dutch adaptation of the Bayley scales was used.[87] Results of the mental and (psycho)motor scales were expressed as standard scores. These scores considered mental and (psycho)motor developmental indexes respectively. The normal range of each index was 100 ±16 (mean ±SD). Classification of the indexes resulted in *low* (≤84), *normal* (85-116) and *high* (≥117). Indexes *≤84 were defined as abnormal.*

Observation session

We videotaped all infants between the third and eighth postnatal day. During the video recording session, infants were placed in supine position, wearing only a loose diaper. They lay under a radiant warmer at a constant temperature of 36.5 °C. Each recording lasted 3 hours: 90 minutes before and 90 minutes after feeding. During observation sessions, neonates had no sedation, needed no ventilatory support, nor did they have infusion lines.
At 6 and 12 weeks of age (±1 week), we videotaped the infants again. During these video recording sessions, infants were placed in supine position, wearing only a loose diaper and body vest. They lay in a box or on a carpet on the floor. Both recordings lasted 15 minutes each.
The infants were observed from above, which is the optimal position to score general movements. In the case of prolonged crying, recordings were interrupted and later resumed in order to obtain similar observation sessions for all infants.
Observation sessions were done at postmenstrual age 37-43 weeks, 43-49 weeks and 49-55 weeks.

Scoring of general movements

The quality of motor behaviour was assessed during playback of the video recording. General movements were selected from the video recordings for analysis. By definition, general movements were series of gross movements of variable speed and amplitude, involving all parts of the body, without distinctive patterning or sequencing of body parts[100] and with a minimal duration of 20 seconds.[68,69]
The state of the infant during its general movement was noted. States were defined as: state A (sleep state): eyes closed, no crying; state B (wakefulness): eyes open, no crying; state C (crying state): crying.[68,69] Since the quality of movement is influenced by vigorous crying, general movements in state C were excluded from analysis. General movements during sucking, hiccups and manipulation were excluded as well.
Items used to assess the quality of general movements are shown in table 2. Definitions of items and their scores are given in table 3.[68,69] Items 1-20 (tables 2, 3) were used to define movement types; items 21, 22 and 23 (tables 2, 3) were each analysed separately.

Observer agreement

Inter-observer agreement to score the isolated items of general movements (table 2), with the exception of items pelvic tilting and hands to midline (table 2; items 22, 23), were determined using kappa statistics, as previously described.[67,111] After training, the determination of pairwise inter-observer agreement (by van Kranen-Mastenbroek and the observer in this study) showed kappa values >0.81 corrected for chance for the scoring of these items. For each of the items pelvic tilting and hands to midline, test tapes were constructed, consisting of 30 general movements randomly selected, with a proportional distribution over the assessed scores. The scores on movements, were used in the determination of the inter-observer agreement together with the other 3 observers: 2 physiotherapists (observers 2, 4) and 1 research fellow (observer 3), (table 4). The observers were not aware of the patient's history. Since the observers were not trained in the scoring of both items, their definitions and scores were provided (tables 2, 3; items 22, 23). Pairwise and group inter-observer agreement corrected for chance for both items were determined.[67,111] Group inter-observer agreement was 0.84 and 0.98 (table 4), respectively.
In this study, all movement items were scored by one observer. For the assessment of the intra-observer agreement, the isolated items of the general movements were scored a second time, after an interval of 4 months (kappa values ≥0.92). The intra-observer agreement of the items pelvic tilting and hands to midline was 1.

Table 4

Pairwise and group inter-observer agreement for items pelvic tilting and hands to midline used in the quality score of general movements.

	observers	1-2	1-3	1-4	2-3	2-4	3-4	group
Item 22	p_o	0.97	0.93	0.93	0.90	0.90	0.87	0.92
	p_e	0.50	0.50	0.50	0.50	0.50	0.50	0.50
	k	0.94	0.86	0.86	0.80	0.80	0.74	0.84
Item 23	p_o	1.00	1.00	0.97	1.00	0.97	0.97	0.99
	p_e	0.50	0.50	0.50	0.50	0.50	0.50	0.50
	k	1.00	1.00	0.94	1.00	0.94	0.94	0.98

p_o= observed agreement, p_e= agreement to be expected by chance when judgements are statistically independent, k= kappa value

Definition of movement types

The selection of representative movement types in the study population was based on 20 items scored per general movement (table 2; items 1-20, chapter 4). All item scores of all general movements per observation session, per infant were fed into a computer database. Analysis of data was performed per observation session. Items that only had one score in a study group were excluded from analysis. Remaining items were used to define movement types. Each different combination of item scores formed one movement type. Percentages of movement types that occurred per infant were calculated. Relevant types for a study group were selected by significant group differences and discriminative power of a particular movement type. Additionally, all movement types that occurred in a study group with a substantial frequency ≥1% were included. In this way, all movement types that could be relevant to a study group were defined.
For each infant per observation session, the repertoire of its movement types was described and formed a movement pattern. Per infant, the quality of spontaneous motor behaviour was studied longitudinally in 3 observation sessions and the developmental course of movement types was described. Since all infants were awake during the observation sessions at follow-up, the developmental course of general movements was studied only in state B (chapters 6, 7).

Statistical analysis

Discriminant analysis was used as a statistical procedure to determine the movement types that best classified infants into one of the groups (SPSS version 7.52).
All data were analysed using non-parametric statistics because the great majority of data appeared to be not normally distributed (Kolmogorow-Smirnov test and Shapiro-Wilk test, SPSS version 7.52).
To analyse differences between study groups, the Kruskal-Wallis H test (analysing groups together) or the Mann Whitney U-Wilcoxon rank sum w test (analysing groups pairwise) were used (SPSS version 7.52).
To analyse differences within a study group during its developmental course, the Kendall test (analysing follow-up periods together) or the Wilcoxon matched-pairs signed-ranks test (analysing follow-up periods pairwise) were used (SPSS version 7.52).
Correlations between variables in each group were determined by calculating the Spearman rank-order correlation coefficient (SPSS version 7.52).
Differences were considered statistical significant for p values lower than 0.05. ■

Chapter 4

Adapted from:
Kingma H., van Hall M.H.J.A., Vles J.S.H., van Kranen-Mastenbroek V.H.J.M., Caberg H.B., Blanco C.E., Troost J. Selection of relevant types of spontaneous movements in infants. Submitted.

Selection of relevant types of spontaneous movements in infants

Abstract

Spontaneous behaviour of full-term neonates and infants is generally classified according to movement types. However, the definition of movement types differs from study to study, hindering comparison of the results. This thesis presents a method that allows researchers in this field to select and quantify movement types that are relevant to the aim of their study. The new classification method is characterised by its discriminative power to divide study groups based on movement types. In this study, spontaneous behaviour was classified in 85 full-term neonates divided into groups based on umbilical artery pH and neurological examination. In the population under survey, 1578 general movements were observed and 20 items were scored for each general movement. The combination of item scores was considered to form a movement type. With many items, many combinations of item scores are possible, resulting in a large number of movement types with a large variety of frequencies distributed over the infants. A choice had to be made between a loss of detail (number of items) versus a loss of quantity (number of classified movements). Reduction of the number of relevant items led to a more manageable number of classified movement types without neglecting too many observed movements. In this way, both relevant items and movement types could be selected and the specific movement patterns of infants could be defined in an objective way.

Introduction

The classification of spontaneous behaviour in full-term neonates and infants is generally based on an assessment of the general movements (movement types) that form a typical movement pattern during an observation session.[21,29,48,58,68,69,100-103] Assessment of the quality of general movements, so as to identify normal and abnormal movement types, was performed by gestalt perception[21,29,48,58,100-103] or by the scoring of different items that characterise a general movement.[67-69] Gestalt perception has proven to be of great clinical value, but requires special clinical expertise and training; the comparison of data might be complicated by observer

variability (various observers or institutes) because the definition of movements (magnitude, type) may differ considerably. The scoring of different items is of interest since the different items that together constitute a general movement -although acting in concert- may be generated by different underlying neuronal structures. Also, a precise description of the classification of these relatively simple items is easier than that of a complex general movement as a whole. Even then, the detailed description of a general movement poses some basic problems.

1. It is practically impossible to define all parameters that completely describe a general movement. The precise definition of a movement, or movement type, already poses a basic dilemma: what is the minimal displacement required to consider it as a movement and to what extent should such a movement be described. Or in physical terms: what is the minimal resolution for a movement to be detected and by how many parameters should it be characterised (e.g. amplitude, velocity, acceleration, direction, evolution in time, etc.). Both resolution and number of descriptive parameters depend on the detection method (e.g. visual observation by a physician versus displacement sensors mounted on the neonate). Most studies make use of visual observation, which requires no complex equipment or manipulation of the neonates.[21,29,44,58,68,69,100-103] Generally, a video recorder is used for data-storage and (re)analysis of the movements of subjects. In the case of visual observation without displacement sensors, inter-observer variability complicates the comparison of data[67] because the definition of a movement (magnitude, type) may differ considerably, as is the case in gestalt perception too.
2. If ever movements can be described by isolated items unambiguously, the question is whether the neuro-motoric status of the subject can be described by these items. The selection of relevant items, movement types and the preservation of coherence in the item scores per general movement requires a special statistical procedure since the items scored are nominal and mutually dependent variables (part of one general movement).

Irrespective of the classification method, an accurate definition of a specific movement pattern per infant is complicated, also, by the fact that both the number and type of movements may vary strongly during an observation session.
The development of a clear method applicable to the selection and quantification of movement types that could be used by all researchers in the field is a need. This method could provide objective interpretation of the data obtained by different groups.
The combination of items, that is the basis of the method used in this thesis, is first presented in an analytical way (see methods) and then, the way in which it was applied on a population of 85 infants (see results) is explained in detail. A simple conversion technique, followed by standard statistical procedures, allowed the proper selection of relevant items and the construction of relevant movement types.

Infants and methods

Infants

Eighty-five full-term infants were studied. Infants were included or excluded according to the criteria described in chapter 3. The group of 85 full-term infants was divided into 3 subgroups: *normal umbilical artery pH* (pH ≥7.20), *intermediate umbilical artery pH* (pH ≥7.10 and <7.20) and *low umbilical artery pH* (pH <7.10). A neurological examination, according to Prechtl[98], was performed on all infants between the third and eighth postnatal day.

Methods

Infants were videotaped between the third and eighth postnatal day. Each recording lasted 3 hours. Recording techniques are described in detail in chapter 3.

Scoring of general movements

General movements, as defined in chapter 3, were selected from the video recordings. Items 1-20, used to describe the quality of general movements, are shown in table 2. Definitions and scores of these items are given in table 3.[68,69] Inter and intra-observer agreement was determined using kappa statistics.[67,113] The incidence of each item was determined.

Analysis

To allow an appropriate analysis, all items were scored into ordinal scales. For example, assuming that arm movement velocity was classified as slow, medium or fast; the transformation into ordinal values was: slow=0, medium=1 and fast=2.

Definition and selection of movement types

The following illustrates the analytical procedure with an example, before the generalized mathematical description is given. Our major problem was how to handle the large amount of movement types represented by the numerous amount of possible combinations of item scores per general movement. The procedure proposed is an analogon of the routine mathematical conversion from a binary into a decimal system. We present a formula that assigns a unique code to a movement type (a kind of bar code) that can be converted back to the original outcome of the items scored without reduction of any information.

Assume for simplicity that only 3 items of a general movement are scored:

Item 1:	0=fast ,	1=slow
Item 2:	0=large,	1=medium, 2=small, 3=tiny
Item 3:	0=good,	1=bad

Only the maximum possible scores per item (here 4) is relevant in order to generate the bar code of the movement types (GM code). This GM code is constructed as follows (note that the maximum number possible scores '4' is used as the base of the formula):

$$\text{GM code} = \text{SCORE}_{\text{ITEM1}} + 4^{\wedge} \text{SCORE}_{\text{ITEM 2}} + 4^{\wedge} 4^{\wedge} \text{SCORE}_{\text{ITEM3}}$$

This results in the following conversion table:

GM code	$\text{SCORE}_{\text{ITEM1}}$	$\text{SCORE}_{\text{ITEM2}}$	$\text{SCORE}_{\text{ITEM3}}$
0	0	0	0
1	1	0	0
4	0	1	0
5	1	1	0
8	0	2	0
9	1	2	0
12	0	3	0
13	1	3	0
16	0	0	1
17	1	0	1
20	0	1	1
21	1	1	1
24	0	2	1
25	1	2	1
28	0	3	1
29	1	3	1

For example, GM code 24 represents the movement type classified as fast, small and bad. Because of the different number of scoring possibilities per item (here for item 1, 2 and 3 respectively 2, 4 and 2), some GM codes do not exist (e.g. GM codes 2, 3, 6 and 7). Statistical analysis of the GM code preserves the coherence of the item scores per general movement, in contrast to a statistical analysis of the separate items.
The conversion procedure can be performed with any number of items with any number of maximum scores. Assume an observer defines k distinguished movement items named $item_1$, $item_2$, $item_3$, ..., $item_{k-1}$, $item_k$. The items may yield an outcome score $SCORE_{ITEMk}$, with m possible scores numbered as 0, 1, 2, 3 ...m-1 (example m=2; 2 possible scores: 0 and 1). The combination of the k item scores form a movement type. Assume now that the maximum number of the item score (observed over all items) is m_{max}. Now the unique movement type score GM code can be generated again by the formula:

$$\text{GM code} = \sum_{i=1}^{i=k} (m_{max})^{i-1} \times SCORE_{ITEMi}$$

$$= SCORE_{ITEM1} + (m_{max}) \times SCORE_{ITEM2} + (m_{max})^2 \times SCORE_{ITEM3} +$$

$$..... + (m_{max})^{k-2} \times SCORE_{ITEMk-1} + (m_{max})^{k-1} \times SCORE_{ITEMk}$$

Now any combination of item scores is represented again by the unique GM code. A large number of items and movement types forces a selection of relevant items and movement types by statistical analysis, which is now possible because of the generation of the GM code.

First, only those items that show variability in the infants investigated are selected. The selected items are then used to generate the GM code that represents all movement types. Subsequently, these movement types are grouped per infant since the number of general movements per infant per observation session varies.

This procedure is a correction for the problem that the number of general movements per infant per observation session varies widely. Then, group differences can be analysed (Kruskal-Wallis H test) and movement types representative of a specific group can be detected by discriminant analysis, both based on the frequency of occurrence of the movement types per infant (SPSS version 7.52). Statistical significance is defined by a p value lower than 0.05.

Results and discussion

Infants were divided into 3 groups based on the 95% confidence intervals:[11] *normal pH* ≥7.20 (30 infants), *intermediate pH* ≥7.10 and < 7.20 (23 infants) and *low pH* <7.10 (32 infants). A total of 1578 general movements were selected. The number of general movements per infant per observation session ranged from 1 to 59 (median 16).

As described in chapter 3, inter-observer agreements on the scores of items 1-20 of general movements (table 2) were determined. Pairwise inter-observer agreement on the scoring of these items showed kappa values >0.81. The intra-observer agreement on the isolated items of general movements was assessed by kappa values ≥0.92.

The frequency distribution of item scores is shown in table 5. Item scores 13, 14, 15, 16, 17, 18 and 19 showed no variation at all (scores were always 1) and were therefore excluded from further analysis. In contrast, item scores 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 20 varied. To conserve the possible correlation between item scores within a general movement, the GM code was generated according to the formula:

$$\text{GM code} = \text{SCORE}_{\text{ITEM1}} + 4 \times \text{SCORE}_{\text{ITEM2}} + 4^2 \times \text{SCORE}_{\text{ITEM3}} + 4^3 \times \text{SCORE}_{\text{ITEM4}} + 4^4 \times \text{SCORE}_{\text{ITEM5}}$$
$$+ 4^5 \times \text{SCORE}_{\text{ITEM6}} + 4^6 \times \text{SCORE}_{\text{ITEM7}} + 4^7 \times \text{SCORE}_{\text{ITEM8}} + 4^8 \times \text{SCORE}_{\text{ITEM9}} + 4^9 \times \text{SCORE}_{\text{ITEM10}}$$
$$+ 4^{10} \times \text{SCORE}_{\text{ITEM11}} + 4^{11} \times \text{SCORE}_{\text{ITEM12}} + 4^{12} \times \text{SCORE}_{\text{ITEM13}}$$

Table 5 *Frequency of occurrence of item scores (n=1587 general movements).*

item 1	0	15.5%
	1	84.5%
item 2	0	.3%
	1	99.7%
item 3	0	11.0%
	1	89.0%
item 4	0	8.0%
	1	8.7%
	2	83.2%
item 5	0	.1%
	1	99.9%
item 6	0	.4%
	1	99.6%
item 7	0	4.1%
	1	95.9%
item 8	0	1.2%
	1	31.6%
	2	67.2%
item 9	0	42.9%
	1	1.7%
	2	11.8%
	3	43.6%

(cont')

item 10	0	1.1%
	1	98.9%
item 11	0	1.2%
	1	98.8%
item 12	0	1.1%
	1	98.9%
item 13	1	100.0%
item 14	1	100.0%
item 15	1	100.0%
item 16	1	100.0%
item 17	1	100.0%
item 18	1	100.0%
item 19	1	100.0%
item 20	0	.1%
	1	99.9%

Maximum 27648 possible different movement types could be theoretically distinguished, of which, however, only 121 different movement types really occurred. All 121 movement types were grouped; the frequency of occurrence of any movement type per infant per observation session was then calculated. By using discriminant analysis and comparison of significant group differences (Kruskal-Wallis H test), the relevant types for either a pH group (normal, intermediate and low) or neurological examination (normal and abnormal), (SPSS version 7.52) were selected. Additionally, all movement types that occurred with a frequency ≥1% were included.

Table 6 shows the 17 movement types that occurred at least 14 times (≥1%). These 17 movement types represented 81.5% of all general movements. For clarity, these 17 movement types were also labelled alphabetically, a to q, according to the frequency of occurrence in table 6. The discriminant and Kruskal-Wallis H analyses indicated that the less frequently (<1%) occurring 104 movement types should not be included for further analysis (no significant differences between the groups and poor classification of the groups).

Table 6 *Frequency of occurrence of the 17 movement types, a to q, that occurred: a) with a frequency of 1% or more, b) with significant different frequencies in the study groups (Kruskal-Wallis H test) or c) contributed to classification of the study groups (discriminant analysis).*

			number	%
GM code	22517141	a	380	24.1%
	22320533	b	301	19.1%
	22304149	c	130	8.2%
	22500757	d	90	5.7%
	22304085	e	58	3.7%
	22517140	f	56	3.5%
	22320532	g	51	3.2%
	22451605	h	40	2.5%
	22500693	i	30	1.9%
	22304133	j	26	1.6%
	22451477	k	25	1.6%
	22320405	l	19	1.2%
	22304148	m	18	1.1%
	22435221	n	17	1.1%
	22500756	o	16	1.0%
	22451604	p	15	1.0%
	22500741	q	14	1.0%

Table 7 *Relation between movement type and item scores.*

		movement type																
		a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q
item 1	0					■		■						■		■		■
	1	■	■	■	■		■		■	■	■	■	■		■		■	
item 2	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 3	0										■						■	
	1	■	■	■	■	■	■	■	■	■		■	■	■	■	■		■
item 4	0											■	■					
	1						■			■								
	2	■	■	■	■	■		■	■		■			■	■	■	■	■
item 5	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 6	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 7	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 8	1			■	■		■			■	■			■	■	■		
	2	■	■			■		■	■			■	■				■	■
item 9	0		■	■			■	■			■		■	■				
	2								■			■			■			■
	3	■			■	■				■						■	■	
item 10	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 11	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 12	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
item 20	1	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

Table 7 shows the relation between the 17 movement types and the item scores: item scores 1, 3, 4, 8 and 9 varied over the 17 movement types selected in contrast to item scores 2, 5, 6, 7, 10, 11, 12 and 20. This shows that only items 1, 3, 4, 8 and 9 contributed to the generation of the 17 different movement types, and that these items and movement types are the major relevant classifying parameters for the general movements. The generation of movement types, using the GM code, and the subsequent grouping (calculation of the relative frequency of occurrence of movement types per infant per observation session), allowed to define the dominant movement types and to describe the movement patterns per infant. Table 8 gives a complete overview of the relative frequency of occurrence of movement types per infant.

Table 8 *Overview of the relative frequency of occurrence of the movement types per infant.*

pH=umbilical artery pH; n.e.=neurological examination (1=normal, 2=suspect, 3=abnormal); n infant=number infant.

		movement type (frequency of occurrence per infant)																	
		pH	n.e.	%a	%b	%c	%d	%e	%f	%g	%h	%i	%j	%k	%l	%m	%n	%o	%p	%q
n infant	1	7.33	1	25				50											25	
	2	7.30	1																	
	3	7.20	1																100	
	4	7.22	1	50								25			25					
	5	7.21	1	67	17		17													
	6	7.23	1	50			13	13											25	
	7	7.28	1	75				25												
	8	7.25	1	100																
	9	7.22	1	30	50	10			10											
	10	7.32	1	80			10					10								
	11	7.21	1	67	33															
	12	7.23	1	73	7		3	3		3				3	7					
	13	7.28	1					100												
	14	7.24	1	100																
	15	7.22	1	63			25					13								
	16	7.32	1	76			18	6												
	17	7.28	1	50	31		13			6										
	18	7.31	1	43	10		10	14			10	5		5			5			
	19	7.24	1	13	44	19				25										
	20	7.26	1	33			33	17										17		
	21	7.24	1	18	36	36												9		
	22	7.23	1	79	14			7												
	23	7.22	1	43		14	14	14									14			
	24	7.30	1		50							17		17	17					
	25	7.26	1	100																
	26	7.31	1	63	4	4	7	7				4	4					7		
	27	7.24	1	64	9	18	9													
	28	7.29	1	55	9		9										27			
	29	7.27	1	41	47	6					6									
	30	7.46	1	54	15	8	23													

(cont')

		movement type (frequency of occurrence per infant)																	
		pH	n.e.	%a	%b	%c	%d	%e	%f	%g	%h	%i	%j	%k	%l	%m	%n	%o	%p	%q
n infant	31	7.18	1	100																
	32	7.19	1	14	10						24			14	5					33
	33	7.17	1	40		10		20				30								
	34	7.17	1	28	56			6		11										
	35	7.19	1	43				14			14									29
	36	7.12	1	46	4		4	13	4	4	8	13						4		
	37	7.11	1					20	20		20			20				20		
	38	7.15	1	28	6	11	11		6	6	6				6	6		6	11	
	39	7.10	1	33	11		44	11												
	40	7.18	1	71			14	14												
	41	7.16	1	38			23	19			12						4	4		
	42	7.19	1	17	33			17					17					17		
	43	7.13	1			14		7		21	21		7	7	7	7	7			
	44	7.17	1		10	40	10			10			20		10					
	45	7.12	1	25			25						50							
	46	7.19	1	33				11		11							11	11	11	11
	47	7.12	1	4	17	13		13		29	4					17		4		
	48	7.19	1	21	17	7	14	14	7	7	7	3						3		
	49	7.19	1	31	38		15			15										
	50	7.12	1	59	11			11			4			7	4				4	
	51	7.10	1	29	12			6			12			29					6	6
	52	7.15	1	8	17	17			8	33					8	8				
	53	7.17	1	25	58			8							8					

(cont')

		movement type (frequency of occurrence per infant)																		
		pH	n.e.	%a	%b	%c	%d	%e	%f	%g	%h	%i	%j	%k	%l	%m	%n	%o	%p	%q
n infant	54	7.02	1	28	34	21			3	3		10								
	55	6.96	1	17	67										17					
	56	6.79	1	80			20													
	57	7.02	1	27	43	7	3		17	3										
	58	6.94	1	17	39	9			26			4	4							
	59	6.86	1	33	11	4	22				7	15						4		4
	60	6.98	1	10	10	23	3		54											
	61	6.97	1	25			50											17		8
	62	7.04	2	27	36	9			9	9									9	
	63	7.07	2	75				25												
	64	7.08	1	7	33	39	7		7		2	2					4			
	65	6.74	1	64			32					5								
	66	7.03	1	13	56	13			6				6		6					
	67	6.93	1			14	57					14						14		
	68	6.95	2		40	40				20										
	69	6.96	1	31		23			15			23	8							
	70	6.99	1	9							36			55						
	71	7.06	1	38	27	3				8	8	3		3	5		5			
	72	7.08	2	40			60													
	73	7.08	2	53	23			10	3		3			3					3	
	74	7.08	1	6	63	6		6						6		6				6
	75	6.83	1	5	65					25							5			
	76	7.02	2	11	41	15			11	4	4				4	7	4			
	77	7.09	2	25	20	20			5	5	5			5	5		10			
	78	7.02	1	24	4		44	8		8		8							4	
	79	6.87	1	50				25				8					8	8		
	80	7.01	1	26	48	9	4	9		4										
	81	7.07	1	71	29															
	82	6.99	1	6	25	23	2	2	13				21		4	4				
	83	7.03	2	12	15	27				4	4		19			19				
	84	6.65	3		33	44				11	4					4				4
	85	6.64	3		78	22														

Conclusion

This study showed that the calculation of the GM code representing a specific movement type offers insight into the frequency of occurrence of any combination of item scores and, therefore, allows the observer to: a) eliminate irrelevant or redundant items b) define movement types and c) describe the relevant movement patterns by standard statistic procedures. The following show the basic methodological procedure:

1. Define study groups.
2. Define and score items relevant to the definition of general movement types; recode nominal variables into ordinal variables.
3. Eliminate items when their scores do not vary within study groups.
4. Generate a unique movement type score using the relevant items; group movement types per infant to correct for the difference in number of general movements per infant per observation session.
5. Determine, by discriminant analysis, which movement types contribute to a good classification of the infants into one of the several study groups; detect types that occur with a significantly different frequency in the study groups; select relevant movement types accordingly. Include all additional movement types that occur with a substantial frequency (≥1%).
6. Exclude items that do not vary from the movement types selected.
7. Repeat this procedure when other study groups are defined or included. ■

Chapter 5

Adapted from:
van Hall M.H.J.A., Vles J.S.H., Kingma H., van Kranen-Mastenbroek V.H.J.M., Caberg H.B., Troost J., Blanco C.E. The influence of umbilical artery pH on the quality of spontaneous general movements in full-term neonates. Submitted.

The influence of umbilical artery pH on the quality of spontaneous general movements in full-term neonates

Abstract

Perinatal hypoxia-ischaemia is a major concern because of the possibility of an acute encephalopathy and long-term neurological disability. The qualitative assessment of general movements is a new non-invasive diagnostic tool used for the early detection of brain dysfunction in newborns. General movements (1578) in 85 full-term newborns within a wide range of umbilical artery pH (6.64-7.46) were studied. The items *amplitude of arms compared to legs* and *fluency* were found to be related to umbilical artery pH. It is known that acute asphyxia may result in lesions primarily confined to the internal capsula and the basal ganglia. The observed clinical findings: less fluent, more tremulous general movements, are in accordance with a dysfunction of these structures.

Introduction

Several conditions are well known to affect the function of the brain. In this context, perinatal hypoxia or ischaemia are a major concern because they may lead to acute encephalopathy and long-term disability.[74] The underlying pathophysiological mechanisms of hypoxia-ischaemia are complex and, unfortunately, no exact indicators of their presence and severity exist. The clinical manifestations of hypoxia-ischaemia are well known: they vary with gestational age, type of hypoxic-ischaemic insult and pattern of neuronal lesion.[18,125] Studies on fetal monkeys have demonstrated that the degree of acidosis during hypoxia-ischaemia is related to the size and site of neuropathological lesions.[95] The immediate consequences of hypoxia-ischaemia and its role in neurological morbidity are difficult to define. Umbilical artery pH has been used to define the degree of hypoxia-ischaemia, but its relation to neurological symptoms is not known. The qualitative assessment of general movements is a new non-invasive diagnostic tool used for the early detection of brain dysfunction in newborns.[29,120] Observation of general movements in both preterm and full-term infants with hypoxic-ischaemic encephalopathy has been reported to be of diagnostic and prognostic value.[103] In this chapter, the quality of postnatal motor behaviour in term born infants is studied in relation to umbilical artery pH and neurological examination.

Infants and methods

Infants

Eighty-five full-term infants were studied. Infants were included or excluded according to the criteria described in chapter 3. The group of 85 full-term infants was divided into 3 subgroups: *normal umbilical artery pH* (pH ≥7.20), *intermediate umbilical artery pH* (pH ≥7.10 and <7.20) and *low umbilical artery pH* (pH <7.10). Serum glucose, calcium and cranial ultrasounds were normal in the group with pH below 7.10.

Methods

A neurological examination, according to Prechtl,[95] was performed on all infants between the third and eighth postnatal day. As described in chapter 3, results of the neurological examinations were divided into the categories *normal* and *abnormal*. Also, a 3 hour videotape recording of each infant between its third and eighth postnatal day was made. Recording techniques are described in detail in chapter 3.

Scoring of general movements

General movements, as defined in chapter 3, were selected from the video recording for analysis. The state of the infant during its general movement was noted: state A (sleep state): eyes closed, no crying; state B (wakefulness): eyes open, no crying; state C (crying state): crying.[68,69] Since the quality of movement is influenced by vigorous crying, general movements in state C were excluded from the qualitative analysis. Items 1-20, used to describe the quality of general movements, are shown in table 2. Definitions of these items and their scores are given in table 3.[68,69] Furthermore, a global assessment per general movement (tables 2, 3; item 21) is given.

Selection of movement types

The procedure for selection of relevant movement types is described in detail in chapter 4. The frequency distribution of item scores as a function of pH is shown in table 9 (see further). Item scores 13, 14, 15, 16, 17, 18, and 19 showed no variation (scores were always 1) and were therefore excluded from further analysis. In contrast, item scores 1, 3, 4, 8 and 9 varied considerably and 2, 5, 6, 7, 10, 11, 12 and 20 to a limited extent. To keep the possible correlation between item scores within a general movement, a code (GM code) per general movement, unique to the combination of the item scores and representing a specific

movement type, was generated. With the 13 items left, a maximum of 27648 possible different general movement types could be theoretically distinguished, of which only 121 different movement types occurred. The different number of general movements per infant introduced a methodological problem. Therefore, all 121 movement types were grouped; the frequency of occurrence of any movement type per infant per observation session was calculated. By using discriminant analysis and comparison of significant group differences (Kruskal-Wallis H test), the relevant types for either a pH group (normal, intermediate and low) or neurological examination (normal and abnormal), (SPSS version 7.52) were selected. Additionally, all movement types that occurred with a frequency ≥1% were included. Items that did not vary from the movement types selected were excluded.

Statistical analysis

The data were analysed using discriminant analysis, Mann Whitney U-Wilcoxon rank sum w test and Kruskal-Wallis H test (SPSS version 7.52). Statistical significance was defined by a p value lower than 0.05.

Results

Figure 1 shows the histogram of umbilical artery pH in the 85 infants included in the study. Three groups were distinguished based on the 95% confidence intervals:[11] *normal pH* ≥7.20 (30 infants), *intermediate pH* ≥7.10 and <7.20 (23 infants) and *low pH* <7.10 (32 infants) and were analysed separately. The neurological examination[9] was normal in 75 and abnormal in 10 infants. All infants with an abnormal neurological examination had low pH at birth. A total of 1578 general movements (state A: n=899; state B: n=679) were selected: 369 general movements in infants with normal pH, 437 general movements in infants with intermediate pH and 772 general movements in infants with low pH.

Figure 1 *Distribution of umbilical artery pH in 85 infants.*

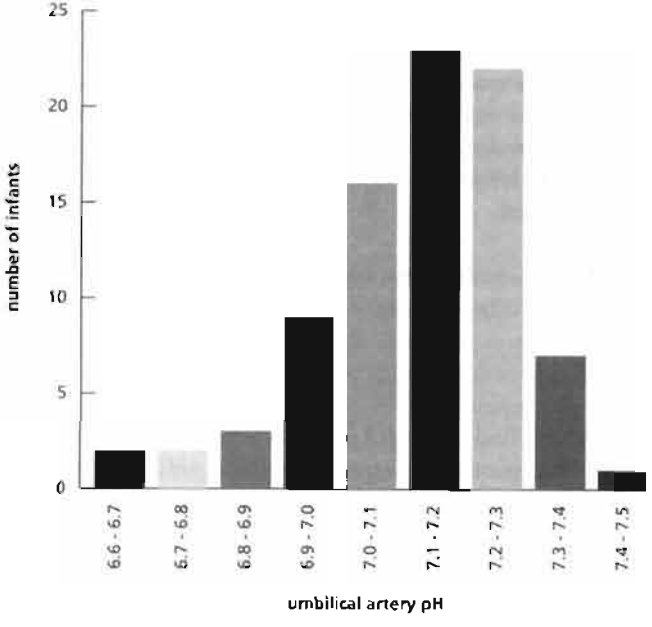


Figure 2 *Histogram of the number of general movements in all infants (n=85).*

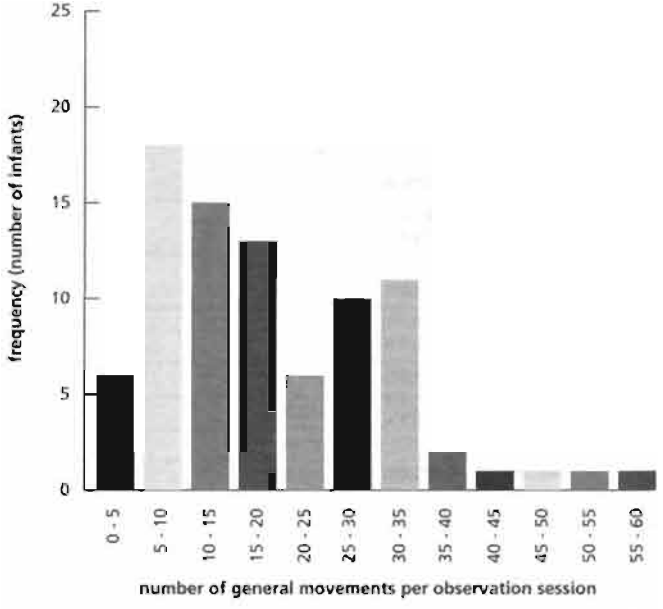


Figure 2 shows the histogram of the number of general movements per infant. The average number of general movements per infant was significantly higher at low pH (mean=24) than at intermediate pH (mean=19) and normal pH (mean=12), (Mann Whitney U-Wilcoxon rank sum w test, p=0.008 and p=0.000). The average number of general movements per infant was not significantly different between infants with an intermediate or normal pH, nor between infants with a normal or abnormal neurological examination (Mann Whitney U-Wilcoxon rank sum w test).

Infants with low pH compared to those with intermediate and normal pH were characterised by general movements with significant ($p < 0.05$) lower speed and smaller amplitude of arms compared to legs (item 4, item 8), less fluency accompanied by more tremulousness (item 9; tables 2 and 9).

Table 9 *Frequency tables of item scores in 85 infants per pH group.*

		umbilical pH		
		low	interm.	normal
item 1	0	9.3%	27.9%	13.8%
	1	90.7%	72.1%	86.2%
item 2	0			1.4%
	1	100.0%	100.0%	98.6%
item 3	0	6.2%	17.6%	13.0%
	1	93.8%	82.4%	87.0%
item 4	0	5.6%	13.3%	7.0%
	1	12.2%	6.2%	4.6%
	2	82.3%	80.5%	88.3%
item 5	0	.1%		
	1	99.9%	100.0%	100.0%
item 6	0	.1%		1.4%
	1	99.9%	100.0%	98.6%
item 7	0	4.0%	2.1%	6.5%
	1	96.0%	97.9%	93.5%
item 8	0	1.0%	.2%	2.7%
	1	38.6%	28.6%	20.3%
	2	60.4%	71.2%	77.0%
item 9	0	58.3%	33.0%	22.5%
	1	1.2%	1.8%	2.7%
	2	8.7%	21.3%	7.0%
	3	31.9%	43.9%	67.8%

(cont')

		umbilical pH		
		low	interm.	normal
item 10	0	.4%	1.6%	1.9%
	1	99.6%	98.4%	98.1%
item 11	0	.5%	1.6%	2.2%
	1	99.5%	98.4%	97.8%
item 12	0	.1%	1.6%	2.4%
	1	99.9%	98.4%	97.6%
item 13	1	100.0%	100.0%	100.0%
item 14	1	100.0%	100.0%	100.0%
item 15	1	100.0%	100.0%	100.0%
item 16	1	100.0%	100.0%	100.0%
item 17	1	100.0%	100.0%	100.0%
item 18	1	100.0%	100.0%	100.0%
item 19	1	100.0%	100.0%	100.0%
item 20	0			.3%
	1	100.0%	100.0%	99.7%

A total of 121 different movement types were observed. Infants with a normal pH showed 52 different movement types, infants with an intermediate pH, 64 different movement types and infants with a low pH, 54 different movement types (not significantly different, $p > 0.05$). Some movement types were present in more than one pH subgroup. Table 10 shows the 17 movement types, a to q, that occurred at least 14 times (≥1%) in relation to item scores. Discriminant and Kruskal-Wallis H analyses indicated that the less frequently (<1%) occurring 104 movement types should be excluded from further analysis (see chapter 4). The 17 movement types represented 82% of all general movements observed. Movement types a, e, g and p occurred significantly more frequently in state A (Mann Whitney U-Wilcoxon rank sum w test, $p < 0.05$).

Table 10 *Relation between the 17 most frequently (≥1%) occurring movement types and item scores.*

		movement type															
		a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q
item 1	0					■		■						■		■		■
	1	■	■	■	■		■		■	■	■	■	■		■		■	
item 3	0										■						■	
	1	■	■	■	■	■	■	■	■	■		■	■	■	■	■		■
item 4	0											■	■					
	1						■			■								
	2	■	■	■	■	■		■	■		■			■	■	■	■	■
item 8	1			■	■		■			■	■			■	■	■		
	2	■	■			■		■	■			■	■				■	■
item 9	0		■	■			■	■			■		■	■				
	2								■			■			■			■
	3	■			■	■				■						■	■	

The frequency of occurrence of the 17 selected movement types was not normally distributed over the infants (e.g. figure 3; movement type a) and the distribution differed markedly from type to type. Most movement types showed an almost binomial distribution; this meant that in most infants no movement type occurred and that in some infants a movement type occurred with a wide range of frequency (e.g. figure 4; movement type g).

Figure 3 *Histogram of frequency distribution of movement type a in all infants (n=85).*

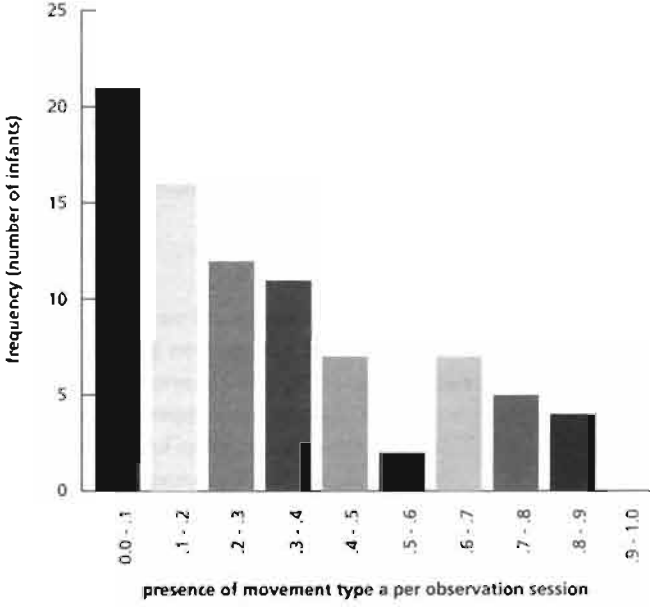
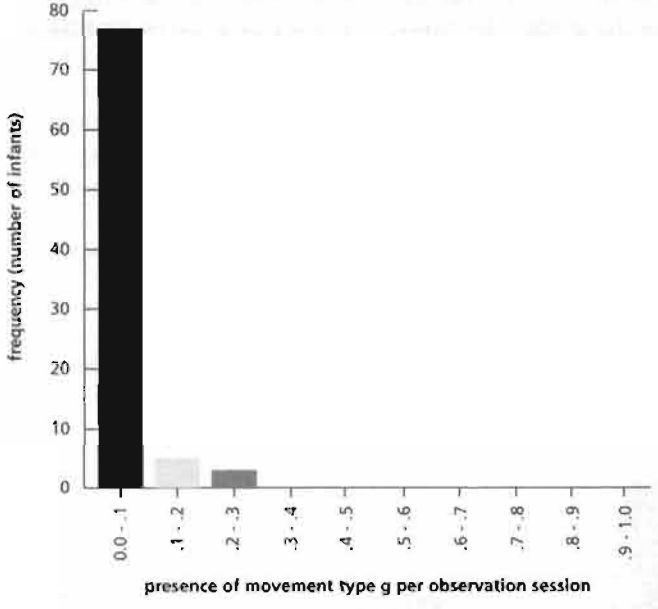


Figure 4 *Histogram of frequency distribution of movement type g in all infants (n=85).*



Based on the comparison of group differences (Mann Whitney U-Wilcoxon rank sum w test), movement type a (smooth onset, slow, equal speed and amplitude of arms compared to legs, fluent) occurred more frequently in the group with normal pH or normal neurological examination than in all other groups ($p < 0.05$). In contrast, movement type b (same as movement type a, but tremulous and not fluent) occurred less frequently in the group with normal pH or normal neurological examination than in the other groups ($p < 0.05$). Movement type c (same as movement type b, but smaller amplitude of arms compared to legs) occurred more frequently in the group with low pH or abnormal neurological examination than in the other groups ($p < 0.05$).
Discriminant analysis, based on the 17 selected movement types, showed that the percentage of infants correctly classified according to their pH subgroup and neurological examination was limited. Only in state B was a good discrimination obtained: 97% of the infants with normal neurological examination and 100% of the infants with an abnormal neurological examination were correctly classified.
A global assessment of all general movements, scored as normal or abnormal (tables 2, 3),[68,69] revealed that in 66 of the 85 infants this score varied over the general movements per infant per observation session.

Discussion

In our study, we found that 5 of 20 isolated items of a general movement were associated with umbilical artery pH and neurological examination: *onset of movement, overall speed, speed of arms compared to legs, amplitude of arms compared to legs* and *fluency*. When movement types were taken, only 2 items of a general movement were associated with umbilical artery pH and neurological examination: *amplitude of arms compared to legs* and *fluency*. Movement types were observed in states A and B, but only in state B, was a good neurological classification possible. This suggests that only general movements scored during wakefulness are relevant to a clinical neurological classification.
In a review on the methodology of the qualitative assessment of general movements in infants, Einspieler et al.[29] described the optimal recording and analysis procedure of general movements. The use of gestalt perception allows a global assessment of the quality of general movements to identify normal and abnormal general movements. The items suggested for this global identification were: complexity, fluency and variability of the general movements. Furthermore, abnormal general movements should be classified in

detail according to amplitude, speed, movement character, sequencing, spatial sectors of the movement, fluency/elegance and onset-offset of general movements.[36] From our data we conclude that irrespective of the method of analysis used, fluency can be used to characterise general movements related to umbilical artery pH. Prechtl et al.[103] observed a loss of variability in the general movements in a group of asphyctic neonates. Our results (less fluent, more tremulous) support the observation that general movements in infants who have suffered an asphyctic insult differ from those in normal infants, and this is probably related to the severity of the hypoxic-ischaemic insult.

The selection criteria for analysis of the general movements (e.g.: the number) is a point of interest. According to Einspieler et al.,[29] in a one hour video recording, 3 sufficiently long general movements - preferably one from the beginning, another from the middle and yet another from the end- should be identified and analysed. One of the arguments for this procedure rests on the assumption that abnormal general movements are consistently abnormal during one recording. However, no data to support this assumption exists. Therefore, we analysed all general movements with a minimal duration of 20 seconds. Our study shows that the number of general movements per infant and per group varied widely, 88% of the infants showed more than one movement type and the global assessment of general movements per infant was inconsistent. These findings agree with a previous study performed by van Kranen-Mastenbroek et al.[89] The clinical relevance of this variability in number of movements, movement types and global assessment of general movements per infant needs further study.[123] Therefore, an assessment of spontaneous motor behaviour based on 3 arbitrarily chosen general movements, as suggested by Einspieler et al.[29] should be considered with caution.

There is no doubt that the qualitative assessment of general movements (normal versus abnormal) using visual gestalt perception is an important, non-invasive practical clinical tool of high reliability and validity to study existing neurological dysfunction and later developmental deficits.[29,102] However, a global assessment of general movements also means a global assessment of the nervous system. Considering that different items of a general movement, although acting in concert, may be generated by different underlying neuronal structures, and that clinical manifestations of hypoxia-ischaemia vary with gestational age, type of insult and pattern of neuronal lesion, studying these items separately is of interest. Therefore, items that differentiated normal from abnormal general movements, and those characterising abnormal general movements in a more detailed analysis,[36] were scored. In our study, the items *amplitude of arms compared to legs* and *fluency* were

found to be related to umbilical artery pH. It is known that combinations of acute, total and prolonged partial asphyxia in full-term neonates result in lesions that are primarily confined to the internal capsule and the basal ganglia.[89,128] The observed clinical findings: less fluent, more tremulous general movements, are in accordance with a dysfunction of these structures. As stated by Prechtl:[101] 'there is still a long way to go before we reach a better understanding of the underlying neuronal processes on which our new neurological assessment method for at risk infants is based'. Thorough observational and neurophysiological studies[47] are still mandatory. Follow-up studies are necessary to determine whether the detailed analysis of general movements, as used in this study, can predict outcome more accurately than other behavioural studies. ■

Chapter 6

Adapted from:
van Hall M.H.J.A., Kingma H., van Kranen-Mastenbroek V.H.J.M., Caberg H.B., Blanco C.E., Troost J., Vles J.S.H. Relation between umbilical artery pH and the developmental course of general movements in full-term infants: a longitudinal study of 67 infants. Submitted.

Relation between umbilical artery pH and the development course of general movements in full-term infants

Abstract

The quality of general movements was studied longitudinally in 67 full-term infants within a wide range of umbilical artery pH. The most frequently occurring movement types were characterised by 5 items: *onset of movement, overall speed, speed of arms compared to legs, amplitude of arms compared to legs* and *fluency.* Most infants showed a wide variety of movement types, irrespective of age. Global assessment varied in most infants initially, but became consistent in time. General movements of infants with an abnormal neurological examination and of infants with a low umbilical artery pH were more tremulous than those of other infants. The observed abnormal quality of general movements in acidosis was not just a transient phenomenon. Follow-up data at 3 months of age showed that asphyxia defined by low umbilical artery pH was correlated with development of postural control. This information is of interest for the acute management of newborns with acidosis post-asphyxia and warrants a careful follow-up for this group of infants.

Introduction

Several studies have shown that fetal hypoxia-ischaemia increases the risk of short and long-term abnormal neurodevelopmental outcome. A proper analysis of the functions of the nervous system requires both a neurological and developmental assessment.[17,48,66,124] Neurological assessment can be achieved by different methods.[43,129] However, whether a neurological examination based on reflexes[6,98] can lead to an appropriate evaluation of all relevant functions of the nervous system is questionable. Based on studies describing functions such as sucking,[137,138] eye movements,[50] facial movements,[93] early reaching[55,56] and leg movements[120] in infants, Wolff[137,138] suggested that these non-reflex functions or spontaneous movements are, probably, clinically more valuable, and should be regarded as complex manifestations of mechanisms involving the nervous system.

The qualitative assessment of spontaneous general movements is a relatively new non-invasive diagnostic tool based on the above mentioned observations, and used for the early detection of brain dysfunction in newborns.[19] According to Prechtl,[120] normal general movements are defined by a variable sequence of arm, leg, neck and trunk movements. They wax and wane in intensity, force and speed and their onset and end are gradual. The majority of extensions or flexions of arms and legs is complex because of superimposed rotations and, often, slight changes in direction of the movements. These components make movements fluent and elegant, creating the impression of complexity and variability.
Because of the large variability -both within and between individuals- in rate of development of different functional abilities, an assessment of the quality of general movements should be repeated at different ages.[29,48] Age of infants and optimal intervals between observation sessions to best study the developmental course of spontaneous motor activity in neonates at risk is not yet standardised. The nature of the adverse condition, transient[14] versus definite[36] (e.g. structural), might be important to the time schedule of the assessment of general movements. In chapter 5, we showed that pH influenced the quality of general movements in full-term neonates in the first postnatal week. However, the influence of pH on the developmental course of general movements is not known.
The aim of this chapter was to provide an accurate description of the developmental course of spontaneous motor behaviour in full-term infants within a wide range of umbilical artery pH.

Infants and methods

Infants

Infants were included and excluded according to the criteria described in chapter 3. The general movements of the infants had to be studied in one particular state. Only state B (wakefulness) occurred at all observation sessions. Therefore, it was possible to study only 67 of the 85 full-term neonates' general movements in state B at each observation session. This group was divided into 3 subgroups: *normal umbilical artery pH* (pH ≥7.20), *intermediate umbilical artery pH* (pH ≥7.10 and <7.20) and *low umbilical artery pH* (pH <7.10).

Methods

Every infant was studied at 3 different observation sessions (t_0, t_1, t_2). At t_0, between their third and eighth postnatal day (37-43 weeks postmenstrual age), a 3 hour videotape recording was made. On the same day, a neurological examination[98] was performed. Furthermore, a 15 minute video recording of each infant at t_1, 5-7 weeks (43-49 weeks postmenstrual age) and at t_2, 11-13 weeks (49-55 weeks postmenstrual age) was made. Following these video sessions, a neurological examination[8] was performed. Recording techniques are described in detail in chapter 3. The results of the neurological examinations were divided into the categories *normal* and *abnormal*, as described in chapter 3.

Scoring of general movements

Only general movements in state B (wakefulness), as described in chapter 3, were selected from the video recordings for analysis. Items 1-20, used to describe the quality of general movements, are shown in table 2. Definitions and item scores are given in table 3.[66,67] Furthermore, a global assessment per general movement (tables 2, 3; item 21) is given. Also, at each observation session (t_0, t_1, t_2), 2 developmental items related to postural control, namely the presence of pelvic tilting and the presence of hands to midline (tables 2, 3; items 22 and 23), were scored. Pairwise and group inter-observer agreement corrected for chance for the scoring of these items was determined, as described in chapter 3.[67,113] Group inter-observer agreement showed kappa values of 0.84 and 0.98 respectively. The intra-observer agreement was 1.

Selection of movement types

The procedure used to select the relevant movement types is described in detail in chapter 4. The frequency distribution of item scores at all observation sessions showed that item scores 13 to 19 (table 11) did not vary (scores were always 1), therefore, they were excluded from further analysis. The remaining 13 items (1 to 12 and 20) were used to generate a movement type.

Table 11

Frequency of occurrence (%) of the scores per item, in relation to postmenstrual age (t_0, t_1, t_2), umbilical artery pH (normal, intermediate and low) and neurological examination (normal, abnormal). Data are not normalized for the different number of general movements per infant.

		occurrence of item scores											
		1st observation session 37-43 weeks postmenstrual age				2nd observation session 43-49 weeks postmenstrual age				3rd observation session 49-55 weeks postmenstrual age			
		normal pH	interm. pH	low pH		normal pH	interm. pH	low pH		normal pH	interm. pH	low pH	
		n=23	n=20	n=24		n=23	n=20	n=24		n=23	n=20	n=24	
				normal n.e.	abnormal n.e.			normal n.e.	abnormal n.e.			normal n.e.	abnormal n.e.
				n=14	n=10			n=18	n=6			n=14	n=10
item 1	0	13.8%	27.9%	10.7%	7.6%	36.1%	35.5%	33.3%	37.0%	40.7%	41.4%	36.6%	34.3%
	1	86.2%	72.1%	89.3%	92.4%	63.9%	64.5%	66.7%	63.0%	59.3%	58.6%	63.4%	65.7%
item 2	0	1.4%											
	1	98.6%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 3	0	13.0%	17.6%	5.6%	7.0%	28.2%	19.6%	4.0%	10.1%	17.7%	14.8%	9.9%	10.8%
	1	87.0%	82.4%	94.4%	93.0%	71.8%	80.4%	96.0%	89.9%	82.3%	85.2%	90.1%	89.2%
item 4	0	7.0%	13.3%	4.4%	7.0%	6.9%	6.5%	1.0%	21.0%	3.5%	11.9%	2.1%	17.6%
	1	4.6%	6.2%	11.7%	12.8%	9.3%	13.1%	5.1%	10.1%	9.5%	14.8%	10.6%	8.8%
	2	88.3%	80.5%	83.9%	80.2%	83.8%	80.4%	93.9%	68.9%	87.0%	73.3%	87.3%	73.5%
item 5	0			.2%									
	1	100.0%	100.0%	99.8%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 6	0	1.4%		2%									
	1	98.6%	100.0%	99.8%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 7	0	6.5%	2.1%	4.4%	3.5%				8.4%				1.0%
	1	93.5%	97.9%	95.6%	96.5%	100.0%	100.0%	100.0%	91.6%	100.0%	100.0%	100.0%	99.0%
item 8	0	2.7%	.2%	1.2%	.9%								
	1	20.3%	28.6%	28.2%	51.6%	56.0%	44.9%	71.7%	60.5%	55.8%	47.6%	61.3%	44.1%
	2	77.0%	71.2%	70.6%	47.5%	44.0%	55.1%	28.3%	39.5%	44.2%	52.4%	38.7%	55.9%
item 9	0	22.5%	33.0%	48.3%	70.8%	14.8%	12.6%	38.4%	12.6%	10.4%	11.4%	16.9%	10.8%
	1	2.7%	1.8%	1.2%	1.2%				1.7%				
	2	7.0%	21.3%	10.0%	7.0%	53.7%	66.8%	49.5%	79.8%	45.9%	53.8%	62.0%	66.7%
	3	67.8%	43.9%	40.6%	21.0%	31.5%	20.6%	12.1%	5.9%	43.7%	34.8%	21.1%	22.5%

(cont')

		occurrence of item scores											
		1st observation session				2nd observation session				3rd observation session			
		37-43 weeks postmenstrual age				*43-49 weeks postmenstrual age*				*49-55 weeks postmenstrual age*			
		normal pH	*interm. pH*	*low pH*		*normal pH*	*interm. pH*	*low pH*		*normal pH*	*interm. pH*	*low pH*	
		n=23	n=20	n=24		n=23	n=20	n=24		n=23	n=20	n=24	
				normal n.e.	abnormal n.e.			normal n.e.	abnormal n.e.			normal n.e.	abnormal n.e.
				n=14	n=10			n=18	n=6			n=14	n=10
item 10	0	1.9%	1.6%	.2%	.6%								2.0%
	1	98.1%	98.4%	99.8%	99.4%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	98.0%
item 11	0	2.2%	1.6%	.2%	.9%								
	1	97.8%	98.4%	99.8%	99.1%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 12	0	2.4%	1.6%		.3%								2.0%
	1	97.6%	98.4%	100.0%	99.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	98.0%
item 13	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 14	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 15	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 16	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 17	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 18	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 19	1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
item 20	0	.3%							.8%				
	1	99.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.2%	100.0%	100.0%	100.0%	100.0%

To keep the possible correlation between item scores within a general movement, a code (GM code) that was unique to the combination of the item scores, and represented a specific movement type, was generated per general movement. With the 13 items left, a maximum of 27648 possible different general movement types could be theoretically distinguished, of which, however, only 99 different movement types occurred. Because of the different number of general movements per infant, all 99 movement types were grouped; the frequency of occurrence of any movement type per infant per observation session was calculated. By using discriminant analysis and comparison of significant group differences (Kruskal-Wallis H test), the relevant types for either a pH group (normal, intermediate and low) or neurological examination (normal and abnormal), (SPSS version 7.52) were selected. Additionally, all movement types that occurred with a frequency ≥1% were included. Items that did not vary over the movement types selected were excluded. In the case of items 22 and 23, group differences related to pH or neurological examination in the interval t_0-t_2 were calculated (Kruskal-Wallis H test).

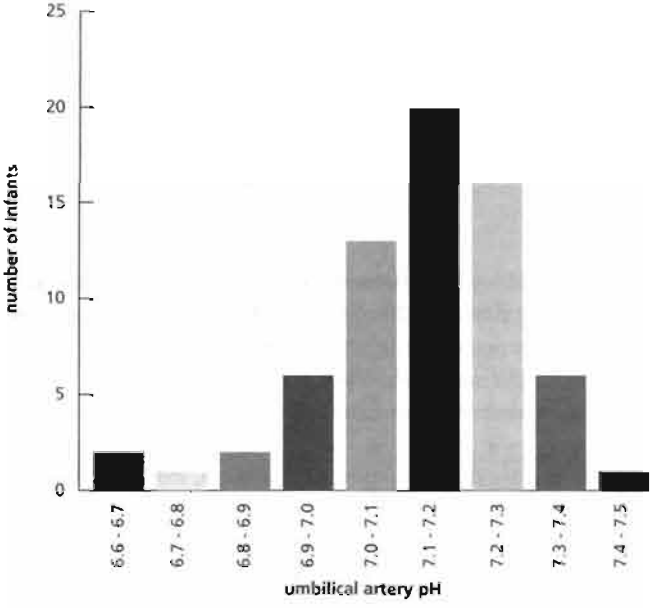
Statistical analysis

The data were analysed using discriminant analysis, Mann Whitney U-Wilcoxon rank sum w test, Kruskal-Wallis H test and Wilcoxon matched-pairs signed-ranks test (SPSS version 7.52). Statistical significance was defined when $p < 0.05$.

Results

Figure 5 shows the histogram of the umbilical artery pH in the 67 infants included in the study.
Three groups were distinguished based on the 95% confidence intervals:[11] *normal pH* ≥7.20 (23 infants), *intermediate pH* ≥7.10 and <7.20 (20 infants) and *low pH* <7.10 (24 infants).
Three observation sessions according to postmenstrual age were defined to allow appropriate statistical analysis: t_0 37-43 weeks (mean 281 days, SD 8), t_1 43-49 weeks (mean 324 days, SD 8) and t_2 49-55 weeks (mean 368 days, SD 10).

Figure 5 *Frequency distribution of the umbilical artery pH of all infants included in the study (n=67).*



Results of the neurological examination are shown in table 12. One of the infants with an abnormal neurological examination showed abnormal tone and suffered seizures. Another had a hemiparesis and also suffered seizures. Both were treated with phenobarbital and serum levels were within normal range at observation session. The other infants were classified as abnormal based on an abnormal tone. At t_3, 611 general movements (mean per infant 9, SD 9), at t_1, 536 general movements (mean per infant 8, SD 3) and at t_2, 533 general movements (mean per infant 8, SD 3) were analysed. Due to the difference in duration of the observation sessions, no conclusion could be drawn from the above data for general movements per observation session.

Table 12 *Results of the neurological examination*

neurological examination	t_0 (n=67)	t_1 (n=67)	t_2 (n=67)
normal	57	61	57
abnormal*	10	6	10

* *All in low pH range*

During the first observation session t_0, the global assessment of general movements, scored as normal or abnormal (tables 2, 3; item 21), revealed that only 28 of the 67 infants showed general movements that were consistently normal or abnormal within one observation session. In contrast, at t_1 (51 infants) and t_2 (53 infants), this variation decreased significantly, showing a consistent score.
Table 11 shows the frequency of occurrence of item scores related to postmenstrual age in the 3 groups under study.
In the interval t_0-t_2, all infants with a normal neurological examination, irrespective of pH subgroups, showed an increase in the frequency of occurrence of items: *onset of movement-abrupt* (item 1-score 0), *amplitude of arms compared to legs-smaller* (item 8-score 1), *fluency-abrupt/jerky* (item 9-score 2) and a decrease in the items *fluency-tremulous* (item 9-score 0), *fluency-fluent* (item 9-score 3), (Wilcoxon matched-pairs signed-ranks test, $p < 0.05$).
At t_0, infants with low pH and abnormal neurological examination showed smaller amplitude of arms compared to legs more frequently than infants with low pH and a normal neurological examination. At t_2, infants with low pH and abnormal neurological examination showed an equal amplitude of arms compared to legs more frequently than infants with low pH and normal neurological examination. This trend was already observed in the second observation session.
Based on 13 items, 99 different movement types (combinations of item scores) occurred. Considering only those types that occurred at least 7 times (≥1%), 28 movement types, a to z3, remained, representing 81% of all general movements observed. The discriminant and Kruskal-Wallis H analyses showed no indication

that the less frequently (<1%) occurring 71 movement types should be included for further analysis (see chapter 4). The relation between these 28 movement types and the 13 selected items showed that items 1, 3, 4, 8 and 9 characterised the movement types (table 13). Scores of the other 8 items did not vary over these movement types. The frequency of occurrence of the 28 selected movement types was not normally distributed over the infants, and the distribution differed markedly from type to type. Most types showed an almost binomial distribution; this meant that in most infants a specific general movement type did not occur and in some infants a specific general movement type occurred, but with a frequency that varied widely from infant to infant.

Table 13 *Relation between movement type and item scores. All other items (items 2, 5, 6, 7, 10, 11, 12 and 20) did not vary over the 28 most frequently occurring movement types: a to z3.*

		movement type																											
		a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q	r	s	t	u	v	w	x	y	z1	z2	z3
item 1	0					■		■						■		■		■	■	■				■			■	■	■
	1	■	■	■	■		■		■	■	■	■	■		■		■				■	■	■		■	■			
item 3	0										■						■			■	■		■	■				■	
	1	■	■	■	■	■	■	■	■	■		■	■	■	■	■		■	■			■			■	■	■		■
item 4	0											■	■													■	■		
	1						■			■												■			■				■
	2	■	■	■	■	■		■	■		■			■	■	■	■	■	■	■	■		■	■				■	
item 8	1			■	■		■			■	■			■	■	■			■	■	■	■	■	■					■
	2	■	■			■		■	■			■	■				■	■							■	■	■	■	
item 9	0		■	■			■	■			■		■	■															
	2								■			■			■			■	■	■	■	■						■	■	
	3	■			■	■				■						■	■						■	■	■	■			■

Table 14

Shading: dominance of movement types per study group.

** significant differences in movement types with respect to neurological examination.*

Frequency of occurrence (fractions) of movement types in relation to observation session, umbilical artery pH and neurological examination. The data are normalized for the different number of general movements per infant before averaging.

occurrence of movement types												
	1st observation session 37-43 weeks postmenstrual age				2nd observation session 43-49 weeks postmenstrual age				3rd observation session 49-55 weeks postmenstrual age			
	normal pH	interm. pH	low pH		normal pH	interm. pH	low pH		normal pH	interm. pH	low pH	
	n=23	n=20	n=24		n=23	n=20	n=24		n=23	n=20	n=24	
			normal n.e.	abnormal n.e.			normal n.e.	abnormal n.e.			normal n.e.	abnormal n.e.
movement type			n=14	n=10			n=18	n=6			n=14	n=10
a	.45	.27	.22*	.11*	.09	.07	.00	.04	.07	.06	.08	.04
b	.11	.10	.29	.21	.04	.05	.11	.02	.03	.01	.14*	.03*
c	.04	.01	.09	.21	.07	.01	.12	.13	.01	.02	.02	.05
d	.06	.08	.08	.14	.04	.01	.04	.02	.11	.04	.02	.03
e	.02	.07	.01	.03	.02	.04	.00	.01	.05	.04	.07	.03
f	.00	.04	.04	.07	.00	.00	.04	.02	.00	.01	.01	.00
g	.01	.03	.02	.00	.01	.02	.10	.02	.01	.03	.03	.00
h	.01	.03	.04	.04	.12	.18	.09	.03	.16	.22	.12	.16
i	.04	.00	.04	.00	.03	.02	.00	.02	.00	.04	.00	.02
j	.02	.05	.01	.07	.03	.00	.00	.00	.01	.01	.00	.00
k	.01	.01	.02	.05	.03	.02	.00	.03	.02	.03	.00	.01
l	.00	.04	.01	.01	.01	.01	.00	.00	.00	.00	.00	.00
m	.00	.00	.01	.02	.01	.01	.05	.03	.03	.02	.06	.03
n	.02	.00	.03	.00	.11	.19	.15	.32	.06	.09	.21*	.12*
o	.01	.01	.02	.00	.05	.01	.01	.00	.11	.03	.01	.01
p	.06	.00	.02	.00	.00	.00	.00	.00	.02	.00	.00	.00
q	.00	.03	.02	.00	.04	.12	.04	.08	.03	.11	.06	.08

(cont')

	occurrence of movement types											
	1st observation session 37-43 weeks postmenstrual age				2nd observation session 43-49 weeks postmenstrual age				3rd observation session 49-55 weeks postmenstrual age			
	normal pH n=23	interm. pH n=20	low pH n=24		normal pH n=23	interm. pH n=20	low pH n=24		normal pH n=23	interm. pH n=20	low pH n=24	
movement type			normal n.e. n=14	abnormal n.e. n=10			normal n.e. n=18	abnormal n.e. n=6			normal n.e. n=14	abnormal n.e. n=10
r	.00	.01	.00	.01	.03	.04	.16	.10	.10	.05	.05*	.10*
s	.00	.03	.00	.00	.06	.04	.07	.03	.02	.04	.03	.06
t	.03	.08	.02	.00	.03	.07	.03	.00	.00	.02	.02	.05
u	.00	.01	.02	.00	.02	.03	.00	.07	.02	.02	.03	.06
v	.02	.03	.00	.00	.04	.01	.00	.00	.06	.01	.00	.00
w	.00	.00	.00	.00	.09	.00	.00	.00	.05	.00	.00	.00
x	.00	.00	.00	.00	.02	.01	.00	.00	.02	.02	.00	.00
y	.01	.00	.00	.01	.00	.00	.00	.00	.00	.01	.00*	.10*
z1	.00	.02	.01	.03	.01	.01	.00	.02	.00	.02	.03	.01
z2	.00	.01	.00	.00	.00	.02	.00	.01	.02	.01	.00	.01
z3	.00	.00	.00	.00	.00	.02	.00	.00	.00	.05	.01	.01

Table 14 shows the frequency of occurrence of movement types related to umbilical artery pH and neurological examination for each observation session.

During the first observation session, some clear cut dominant movement types were observed (types a, b, c and d) related to pH. In the second observation session, other movement types dominated: types c, h, n, q and r. In the third observation session, general movement types b, d, h, n, o, q, r and y were more frequently observed. Changes in dominance of general movement types were also seen for the different pH categories separately.

Characteristics of infants with a normal neurological examination.

The frequency of occurrence of movement types a, b, d, h, n, o and r in infants with normal pH and normal neurological examination changed significantly with age: i.e. at t_5, types a and b were dominant, at t_1, types h

and n were more often observed and at t_2, types d, h, o and r were dominant (Kruskal-Wallis H test, $p < 0.05$).
The frequency of occurrence of movement types a, h, n, q in infants with intermediate pH and normal neurological examination changed significantly with age: i.e. at t_0, type a was dominant whereas at t_1 and t_2 types h, n and q were more frequently observed (Kruskal-Wallis H test, $p < 0.05$).
The frequency of occurrence of movement types b, h, n and r in infants with low pH and normal neurological examination changed significantly with age: i.e. at t_0, type b was dominant, at t_1, types n, r were more often observed and at t_2 types b, h and n were dominant (Kruskal-Wallis H test, $p < 0.05$).

To summarise: with age, in infants with a normal neurological examination, the major difference in general movements shown between the 3 different groups was characterised by the items: *onset of movement, amplitude of arms compared to legs* and *fluency*. Within these items, a change in one movement type was sometimes compensated by a change in another movement type. In infants with normal pH, general movements changed from smooth to abrupt onset, from fluent to jerky and the amplitude of arms compared to legs changed from equal to smaller. In infants with low pH, general movements changed from tremulous to jerky but in both groups, infants with normal and low pH, the onset of movement changed from smooth to abrupt and the amplitude of arms compared to legs changed from equal to smaller.

Characteristics of infants with an abnormal neurological examination.

All infants with an abnormal neurological examination had low pH at birth. At t_0, the dominant movement types were b, c, and d. General movement type a occurred less frequently than in low pH neurological normal infants. At t_1, movement type c remained dominant. Longitudinal evaluation indicated that types a, b, c and d almost disappeared, whereas types h, n, r and y occurred with increasing frequency. At t_2, significant differences were observed between infants with an abnormal neurological examination and infants with a normal neurological examination and a low pH, regarding types b, n, r and y.

To summarise: the difference between infants with a low pH and a normal neurological examination and those with a low pH and an abnormal neurological examination was characterised by the items: *amplitude of arms compared to legs* and *fluency*. Within these items, a change in one movement type was sometimes compensated by a change in another movement type. On average (for the whole group), this resulted in the following: at t_0, infants with an abnormal neurological examination showed more tremulous general movements than infants with a normal one. At t_2, infants with an abnormal neurological examination showed an equal amplitude of arms compared to legs more frequently than infants with a normal one.

Discriminant analysis was performed to establish which movement types contributed to an optimal neurological discrimination between normal and abnormal infants. Using the outcome of the neurological examination of the third observation session as indicator for normality, 97% of the neurologically normal infants and 82% of the neurologically abnormal ones could be correctly classified. The relevant movement types for this classification were c, d, k, m, n, u and y. This meant that the items *onset of movement*, *speed of arms compared to legs*, *amplitude of arms compared to legs* and *fluency* were essential.
Irrespective of pH, the frequency of occurrence of the items *pelvic tilting* and *hands to midline* increased with age in neurologically normal infants. No developmental trend was observed in neurologically abnormal infants (Kruskal-Wallis H test).

Discussion

The results of this study indicated that the most frequently occurring movement types were defined by 5 items, with 4 of them characterising the differences between the various groups under study, i.e. related to neurological examination and umbilical artery pH.
At 37-43 weeks postmenstrual age (t_2), general movements of infants with an abnormal neurological examination and infants with low umbilical artery pH were more tremulous than those of other infants. Twelve weeks later (t_3) no clear cut differences between the general movements were observed in relation to pH. In contrast, infants with an abnormal neurological examination showed an equal amplitude of arms compared to legs more frequently than infants with normal ones. Discriminant analysis showed that normality versus abnormality could be correctly classified by the movement types observed.
Most infants showed a wide variety of movement types irrespective of age. Global assessment showed a different aspect: item scores varied in most infants initially, but became consistent in time. This seeming discrepancy might be explained by the observation that the tremulous aspect decreases in time and is a dominant feature of global assessment.

We propose the following interpretation:

1. Tremulous aspects of general movements appear at the initiation and during the course of a movement, which suggests a cerebellar dysfunction or immaturity.[17]
2. The observed differences in amplitude suggest a dysfunction without precise localisation.
3. The observed differences referred to (voluntary) postural activities (pelvic tilting and hands to midline) suggest an additional cortical component since the cortex is primarily involved in the voluntary initiation of movements.

The effect of hypoxia on the quality of general movements was studied in various groups of high-risk infants.[28,30,103] The same qualitative change in general movements, namely an increased frequency of occurrence in tremulousness, was observed despite different pathogenesis, duration and severity of hypoxia or ischaemia in full-term infants with asphyxia, in 1 to 6 months old infants with repeated apnoeas during sleep, and in 2 and 6 months old infants with apparent life threatening events. Our results, obtained from a group of full-term infants with different degrees of acidosis at birth, are consistent with the literature[103] and corroborate the above mentioned observations. Acidosis interferes with the quality of general movements since an increase in tremulousness was observed. The observed abnormal quality of general movements due to acidosis was not of transient consequences. Follow-up data at 49-55 weeks postmenstrual age showed that acidosis influenced the development of postural control.

Several authors[29,35,103] have suggested that the study of the developmental course of general movements per infant might predict neurological outcome better than the study of group differences. Although we studied and analysed the longitudinal as well as the cross-sectional aspect, inconsistency in the global assessment of general movements in infants hampered a straightforward interpretation on the developmental course of the quality of general movements per infant. A remarkable observation was that this inconsistency in assessment decreased with age. Which and how many of the observed general movements per infant per observation session should be scored, incorporated and taken into consideration for a final assessment has never been studied. Researchers that use global gestalt perception, usually select 3 general movements and give an overall score (global score) for normality.[29] Incorporating all general movements and scoring them separately (normal versus abnormal) introduces a problem similar to that of applying an (micro) analytic approach[58] rather than the global gestalt perception to study general movements. The selection of relevant general movements needs further study.

There is an ongoing debate on whether the most appropriate way to analyse the quality of spontaneous motor behaviour of preterm and full-term infants should be a global assessment[29,73,101] or a detailed analysis. Although both analyses were performed in our study, the main interest was focused on a detailed analysis of the separate items. By using such a detailed analysis, we faced the same problem as Pratt[58] did when he studied the newborn plantar response in detail: a very large number of different possible combinations of item scores occurred. However, ultimately, only 5 items defined the most frequently observed general movement types. The conversion technique we applied (generating GM codes and grouping) reduced the relevant movement types down to 28. Analysis of these 28 movement types indicated that only 5 items were relevant regarding the differences between these movement types. This condensed information now allowed a comparison with Prechtl's gestalt perception method.[100,101] Our results showed an increase in the frequency of occurrence of the item score jerky with age, agreeing with Hopkins and Prechtl,[58] who observed an increase in saccadic quality (jerky, zigzag movements).

A number of studies[46,68,69,123,127] do not provide clinically relevant information[101] since they employed other criteria to assess early spontaneous motor behaviour in infants than global gestalt perception (e.g. variability in preterm infants,[123] details of general movements in small for gestational age infants related to outcome,[68,69] categorization of types of general movement abnormalities based on EMG recordings[46]). From a clinical point of view, because of the differences in methodology some of the results are not similar and allow no insight into the neural mechanisms and neuronal structures involved. However, the relationship between nature, localisation of lesion and type of dysfunction, as expressed by abnormal general movements during the newborn period, and ultimate outcome is poor.[58] Unilateral lesions do not express asymmetry of general movements, they express bilateral changes in the quality of general movements. Abnormal quality of general movements in the full-term infant may not only predict cerebral palsy (monoplegia, diplegia, hemiplegia or quadriplegia) but also mental and/or motor retardation. Therefore, evaluation of the quantitative aspects[15,127] of general movements (comparison of right/left, upper/lower limb motility) should be considered as an extra tool to predict outcome.

In conclusion:

the conversion technique (GM coding) applied in our study allows the comparison of gestalt perception with a detailed analysis of general movements. Asphyxia, represented by acidosis, influences spontaneous motor behaviour in the first week after birth and delays postural control. This information might be of interest for the development of strategies in the acute management of the newborn and warrants a careful follow-up for this group of infants. ■

Chapter 7

Adapted from:
van Hall M.H.J.A., Knigma H., Ghys A., van Kranen-Mastenbroek V.H.J.M., Caberg H.B., Blanco C.E., Troost J., Vles J.S.H. Umbilical artery pH, Apgar score, development of spontaneous motor behaviour in relation to neurological and developmental outcome at 18 months of age in full-term infants. Submitted.

Umbilical artery pH, Apgarscore, development of spontaneous motor behaviour in relation to neurological and developmental outcome at 18 months of age in full-term infants

Abstract

The spontaneous motor behaviour of 63 infants was studied in relation to umbilical artery pH (6.64-7.46) and neurodevelopmental outcome at 18 months of age assessed by neurological examination and Bayley Scales of Infant Development. No clear cut correlation between umbilical artery pH and outcome parameters at this age was found. The same repertoire of movement types, defined by the items *onset of movement, speed, speed of arms compared to legs, amplitude of arms compared to legs* and *fluency* (chapter 6) were relevant. Movement types, observed longitudinally in the first 3 months of life, allows a correct evaluation of an infant's long-term neurodevelopmental outcome. No characteristic movement types related to pH or long-term outcome were found. Two infants with the lowest umbilical artery pH and a clinical encephalopathy had the worst neurological outcome at 18 months of age. Early onset encephalopathy may have more clinical relevance than pH or spontaneous motor behaviour related to abnormal long-term neurodevelopmental outcome.

Introduction

The only objective means to diagnose fetal asphyxia at delivery is by measuring the umbilical artery blood acid-base.[62] Several studies have been carried out to investigate the immediate consequences of perinatal acidosis and the long-term neurological outcome of preterm,[37] full-term[25] and small for gestational age acidotic born babies.[85] Although all studies used different cut off points for umbilical artery pH values to define acidosis (respectively mean ±1 SD, mean ±2 SD or pH <6.9),[91,92,114] their overall results suggest that perinatal acidosis, as measured from the umbilical artery at birth, used as single parameter is a poor predictor for perinatal brain damage and long-term outcome. Therefore, other indicators of fetal asphyxia such as meconium staining of the amniotic fluid,[88] abnormal fetal heart rate patterns,[61] low Apgar scores at 1 and

5 minutes after birth,[83] degree of base deficit and lactate concentration were added, resulting in different scoring systems.[3,19,75,94] The results of these studies are not conclusive. Carter et al. showed that these scoring systems might be useful to identify the full-term and near term infants at risk of multiple organ system morbidity shortly after acute perinatal asphyxia. However, it is probably not the best way to assess the short-term neurological prognosis.[19] Wayenberg et al. suggested that evaluating consciousness, respiration and neonatal reflexes would be a much better predictive tool for short-term neurological outcome.[134]
Hopkins and Prechtl '84 introduced another procedure to predict neurological outcome,[102] the assessment of the quality of general movements in fetuses, preterm and full-term infants and applied this method to a group of asphyctic full-term infants.[103] Using a more detailed method of analysis than that described by Prechtl et al.,[29,35,101] our study also describes the qualitative aspects of early spontaneous motor behaviour in a group of full-term infants within a wide range of umbilical artery pH in relation to neurological and developmental outcome at 18 months of age.
To enable the early identification of infants at risk of neurological morbidity who might eventually need therapeutical intervention, we addressed the following questions:

1. What is the relation between neurological developmental outcome and umbilical artery pH?
2. Can the study of spontaneous motor behaviour in the first 3 months of life predict neurological and developmental outcome?

Infants and methods

Infants

Infants were included and excluded according to the criteria described in chapter 3. Neonatal characteristics and outcome variables in 85 full-term infants were studied at different follow-up sessions. Seven infants were lost to follow-up at 18 months of age, therefore, 78 infants remained.
The general movements of the infants had to be studied in each particular state. At 6 and 12 weeks of age, only state B (wakefulness) occurred at all observation sessions. Only 67 of the 85 full-term infants studied in the first week of life presented wakefulness at each observation session (chapter 6). Sixty-three of these 67 infants were studied in relation to neurological and developmental outcome at 18 months of age. This group

was divided into 3 subgroups: *normal umbilical artery pH* (pH ≥7.20), *intermediate umbilical artery pH* (pH ≥7.10 and <7.20) and *low umbilical artery pH* (pH <7.10). Four infants were lost to long-term follow-up: pH ≥7.20 (2 infants), pH ≥7.10 and <7.20 (1 infant), pH <7.10 (1 infant). Neonatal characteristics (see further, table 15) as well as outcome variables at different follow-up sessions (see further, table 16) for the group of 78 infants compared with the group of 63 infants that served for final analysis were similar in all pH subgroups.

Methods

Every infant was studied at 5 different postnatal ages: t_0, t_1, t_2, 9 and 18 months of age.
At t_0, between their third and eighth postnatal day, a 3 hour videotape recording was made. On the same day, a neurological examination[76] was performed. At t_1 and at t_2, respectively 5-7 weeks and 11-13 weeks after the first videotape recording, a 15 minute video recording of each infant was made. After these video sessions, a neurological examination[6] was performed. Recording techniques are described in detail in chapter 3. Three observation sessions according to postmenstrual age were defined: t_0 37-43 weeks, t_1 43-49 weeks, t_2 49-55 weeks.
At 9 and 18 months of age, a neurological examination[6] and the Dutch adaptation of the Bayley Scales of Infant Development[10,87] to score mental and psychomotor developmental indexes (MDI, PDI) were performed. As described in chapter 3, the normal range of each index was 100 ±16. The indexes were divided in 3 categories: *low* (≤84), *normal* (85-116) and *high* (≥117). Indexes *≤84 were defined as abnormal.* The results of all neurological examinations were divided into *normal* or *abnormal*, as described in chapter 3.

Scoring of general movements

Only general movements during wakefulness, as defined in chapter 3, were selected from the video recordings for analysis. Items 1-20, used to describe the quality of general movements, and items 21, 22 and 23, which were analysed separately, are shown in table 2. Definitions and item scores are given in table 3.[68,69]

Selection of movement types

The procedure used for selection of relevant movement types, based on items 1-20 (tables 2, 3), is described in detail in chapter 4. The 13 items (1 to 12 and 20) presenting varying scores (chapter 6) were used to define a movement type. To keep the possible correlation between item scores within a general movement, a code (GM code) that was unique to the combination of item scores, and represented a specific movement type, was generated per general movement. Ninety-nine movement types (chapter 6) occurred. Because of the different number of general movements per infant, all 99 movement types were grouped; the frequency of occurrence of any movement type per infant per observation session was calculated. By using discriminant analysis and comparison of significant group differences (Kruskal-Wallis H test), relevant types for a pH group (normal, intermediate and low), neurological examination at t_0, t_1, t_2 (normal and abnormal), neurological or developmental assessment at 18 months of age (normal and abnormal), (SPSS version 7.52) were selected. Additionally, all movement types that occurred with a frequency ≥1% were included. Concerning items 21, 22 and 23 (tables 2, 3), group differences related to pH (normal, intermediate, low), neurological examination at t_0, t_1, t_2 (normal versus abnormal), neurological or developmental outcome at 18 months of age (normal versus abnormal) were calculated.

Statistical analysis

The data were analysed using discriminant analysis, Mann Whitney U-Wilcoxon rank sum w test, Kruskal-Wallis H test and Spearman rank-order correlation coefficient (SPSS version 7.52). Statistical significance was defined by a p value lower than 0.05.

Results

Three groups of infants were distinguished based on the 95% confidence intervals:[111] *normal pH* ≥7.20 (21 infants), *intermediate pH* ≥7.10 and <7.20 (19 infants) and *low pH* <7.10 (23 infants).
Table 15 shows the characteristics of the 63 infants included in this study. A moderate correlation was observed between the umbilical artery pH and the Apgar score at one minute (Spearman rank-order correlation coefficient <0.72 at a significant level of p <0.01).

Table 15 *Neonatal characteristics in 3 groups of infants with different umbilical artery pH.*

	pH ≥7.20 n=21	pH ≥7.10 and <7.20 n=19	pH <7.10 n=23
pH**	7.26 ±0.06	7.17 ±0.03	7.01 ±0.13
base excess** (mmol/l)	-4.60 ±1.9	-8.40 ±2.1	-15.00 ±5.11
pCO_2** (kPa)	6.45 ±1.04	7.50 ±1.42	9.78 ±1.88
pO_2 (kPa)	2.39 ±1.21	2.60 ±1.68	1.57 ±1.13*
Apgar score, 1 minute	9 (5-10)	9 (7-10)	5 (1-9)*
Apgar score, 5 minutes	10 (8-10)	10 (8-10)	8 (4-10)*
meconium in amniotic fluid	0%*	21%	22%
birth weight (grams)	3520 ±374	3405 ±479	3130 ±569
gestational age (days)	281 ±6	279 ±6	280 ±10

median ±SD, median (range)
** significant differences compared to the two other groups, Mann Whitney U-Wilcoxon rank sum w test*
*** significant differences between all groups, Mann Whitney U-Wilcoxon rank sum w test*

Table 16 shows the outcome of the neurological examination as well as the Bayley mental and psychomotor score in the different pH groups. A normal umbilical artery pH and Apgar score at one minute seemed to be associated with a higher Bayley mental and psychomotor score and a normal neurological examination (for pH, see figure 6). No clear cut correlation between umbilical artery pH or Apgar scores and outcome parameters was found (Spearman rank-order correlation coefficient lower than respectively 0.44 and 0.50, $p < 0.05$).

Infants with an abnormal neurological examination in the first 3 months of life, represented by an abnormal tone, showed either recovery or persistence of this sign, sometimes accompanied by a discrete motor delay at 9 and/or 18 months of age. One of the infants classified as abnormal because of initial abnormal tone and seizures showed axial hypotonia and motor retardation later. Another infant presenting a hemiparesis and seizures postnatally showed axial hypotonia, tetraplegia and motor retardation later.

Table 16 *Outcome variables at different ages in 3 groups of infants with different umbilical artery pH.*

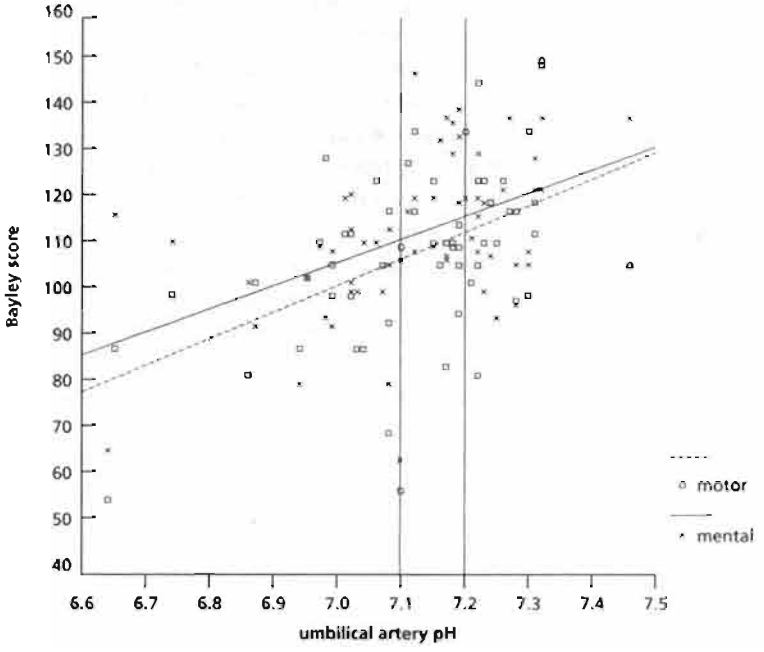
	neurological examination					
	pH ≥7.20 n=21		**pH ≥7.10 and <7.20 n=19**		**pH <7.10 n=23**	
	normal n.e.	abnormal n.e.	normal n.e.	abnormal n.e.	normal n.e.	abnormal n.e.
37-43 weeks pma	100%	0%	100%	0%	61%, n=14	39%, n= 9
43-49 weeks pma	100%	0%	100%	0%	74%, n=17	26%, n= 6
49-55 weeks pma	100%	0%	100%	0%	57%, n=13	43%, n=10
9 months ±1 week	100%	0%	100%	0%	61%, n=14	39%, n= 9
18 months ±1 week	100%	0%	100%	0%	65%, n=15	35%, n= 8

pma=post menstrual age

	Bayley scores 9 months					
	pH ≥7.20 n=21		**pH ≥7.10 and <7.20 n=19**		**pH <7.10 n=23**	
	median (range)	index ≤84	median (range)	index ≤84	median (range)	index ≤84
MDI	106 (86-123)	0	104 (74-127)	1	104 (68-130)	2
PDI	102 (55-123)	2	98 (65-140)	3	100 (56-127)	8
	Bayley scores 18 months					
MDI	118 (92-137)	0	118 (60-147)	1	101* (62-120)	3
PDI	116 (79-150)	1	109 (53-134)	2	97* (51-128)	3

* *p <0.05, Mann Whitney U-Wilcoxon rank sum w test*
MDI=mental developmental index
PDI=psychomotor developmental index

Figure 6 *Bayley scores as a function of umbilical artery pH.*



At t_0, t_1 and t_2, 585, 505 and 496 general movements (mean per infant 9 (SD 9), 8 (SD 3), 8 (SD 3)) were analysed respectively. Due to the difference in duration of the observation sessions, no conclusion could be drawn from the above data for general movements per observation session.
Thirteen infants (1 infant with pH ≥7.20, 2 infants with pH ≥7.10 and <7.20, 10 infants with pH <7.10) were classified as abnormal either by neurological outcome or by 1 of the 2 Bayley scores at 18 months of age. Only 2 infants had both an abnormal neurological examination and low scores for both developmental scales. Discriminant analysis, using neurological outcome and Bayley scores, indicated that no reliable classification for abnormal infants could be achieved based on the frequency of occurrence of all possible item scores (tables 2, 3; items 1-12, 20), global assessment (item 21) or items related to postural control (items 22, 23), (0 to 88% correct classifications, n=4 to 8). In contrast, the majority of normal infants were correctly classified (88 to 100%, n=55 to 59). This result was achieved by analysing item scores obtained at the 3 observation sessions separately, and also by analysing data of all sessions simultaneously, introducing the longitudinal data.
Movement types were defined based on the 13 varying item scores. Ninety-nine movement types occurred. Selecting only types of movements that occurred more than 7 times (≥1%), 28 movement types named a to z3 remained, representing 81% of all general movements. Discriminant and Kruskal-Wallis H analyses showed no indication that the less frequently occurring movement types (<1%) should be included for further analysis (chapter 4). Analysis of the relation between these 28 movement types and the 13 selected items showed that items 1, 3, 4, 8, 9 characterised the movement types (table 13); the other 8 items did not vary over the movement types.
Discriminant analysis using neurological outcome or Bayley scores indicated that a reasonable classification of both normal and abnormal infants could be achieved based on the movement types observed at all 3 observation sessions. The relevant movement types were a to n, which detected 100% of the normal and abnormal infants correctly, with respect to neurological examination, Bayley mental or psychomotor score. When the data of the observation sessions were analysed separately, discrimination power decreased. The relevant general movements indicated that items 1, 3, 4, 8, 9 were all pertinent to a correct characterisation. Individual data of all infants showed a large variability with respect to the occurrence of item scores or movement types. The number of different types per infant per session varied from 1 to 8. Therefore, no characteristic movement types could be found with age (no clear cut developmental aspect) related to pH or outcome (Kruskal-Wallis H test).

Irrespective of pH or neurological examination, no differences in global assessment (tables 2, 3; item 21) or development of postural control (items 22, 23) were found when assessing neurodevelopmental outcome at 18 months of age (Kruskal-Wallis H test).

Discussion

Neither the degree of acidosis nor the Apgar score had clinical relevant predictive value for neurological outcome or Bayley score at 18 months of age. The low predictive value was mainly caused by the high number of infants with a low pH and a normal outcome (13 out of 23). Blood gas analysis after birth in the low pH group indicated that the infants recovered from the acidosis within 60 minutes (table 17). The fact that only 2 infants showed a mild encephalopathy and no multiorgan failure led to the conclusion that the infants included in this study did not suffer from severe asphyxia. This might account for the high rate of normal infants in the low pH group.

Table 17 *Capillary blood gases at one hour of life in infants born with pH <7.10 (n=23).*

capillary blood gases at one hour of life	
pH	7.23 ±0.14
base excess (mmol/l)	-8.80 ±5.19
pCO_2 (kPa)	6.30 ±1.89
pO_2 (kPa)	6.20 ±1.25

median ±SD

Remarkably, the most abnormal neurological examinations at 18 months of age were observed in the 2 infants with the lowest pH values and clinical encephalopathy. This indicates that early onset encephalopathy had a higher clinical relevance than pH or Apgar score for outcome and that therefore, it can be used to identify infants who might benefit from early therapeutic interventions.

The low predictive value was also caused by the presence of 1 infant with a normal pH and 2 infants with an intermediate pH that showed 1 or 2 abnormal Bayley scores.
Results indicate that outcome is best predicted by movement types observed at different ages. Cross-sectional data or separately scored items showed to be worse predictors, irrespective of age. The relevant movement types were described by items 1, 3, 4, 8, 9 in agreement with previous observations (chapters 5, 6).
Prechtl et al.[103] studied the predictive value of general movements in 26 full-term infants with an umbilical cord or neonatal pH <7.10. The incidence of abnormal outcome was 54% compared to 43% in our study. Although 43% of our acidotic infants (pH <7.10; 10 out of 23) were found to be abnormal either by neurological outcome or by one of both Bayley scales at 18 months of age, only 2 of them showed overall abnormal findings while 8 infants showed only one abnormal outcome parameter. Prechtl et al. showed that the item tremulousness, observed in the first 2 weeks after birth, was the best predictor (80% unfavourable outcome).[103] Although initially tremulousness was significantly more often observed in the group of infants with a low pH in our study, the predictive value for abnormal outcome was poor. The difference in results with Prechtl et al. cannot be explained by a difference in degree of acidosis, but it is probably related to the degree of hypoxic-ischaemic encephalopathy included in the group of Prechtl et al. Only 2 of our infants showed clinical signs of early mild hypoxic encephalopathy, whereas 13 infants with severe and 13 infants with mild to moderate post-asphyctic encephalopathy were included by Prechtl et al.[103] Prechtl's[103] observation that the individual trajectory of development of the quality of a general movement is related to outcome is confirmed by our study.
Also studies in other groups of neonates at risk[14,36] have shown that the study of quality of spontaneous motor activity is of great value to predict later neurological outcome and that it is an excellent method for an early selection of infants at risk.
In a review concerning interventions for perinatal hypoxic-ischaemic encephalopathy Vannucci et al.[126] stated that at present no agent has been proven useful to ameliorate perinatal hypoxic-ischaemic brain damage. This might be due to the limited time window for potential therapeutic intervention, which is likely to be no more than 2 to 6 hours after the insult. Therefore, an early identification of infants at high risk of permanent brain damage is critical to the detection of those who might benefit from early therapeutic interventions.

The observation that the 2 children who suffered neonatal seizures later showed the most severe abnormal neurological outcome support Shankaran's[115] statement that early onset encephalopathy is the most relevant single predictor of long-term outcome after acute perinatal asphyxia. Prechtl et al.[103] also indirectly showed a strong correlation between the degree of hypoxic-ischaemic encephalopathy and outcome. Further studies are needed.

Reviewing the literature, acidosis seems to have an impact on outcome: mortality rates ranged from 12 to 33% and morbidity rates from 29 to 60%.[126] Comparison with reported outcomes is often difficult to establish because of variations in timing, categorisation or description of the examinations. Various developmental assessment methods have been used in order to determine developmental outcome. Essential factors for the use of these methods are: appropriate age for each method and expertise in those who administer it. Since it is in studies that include long-term follow-up assessment that the most relevant data is provided, our study needs to be validated by longer follow-up studies evaluating long-term morbidity.

In conclusion: we found that:

1. acidosis alone is not predictive of outcome;
2. low Apgar score is not associated with increased sequelae;
3. outcome is best predicted by movement types observed at different ages;
4. infants with a hypoxic-ischaemic encephalopathy soon after birth have the highest risk of permanent brain damage. ■

Chapter 8

Summary and conclusions

Fetal ischaemia and hypoxia (asphyxia) are a threat to the fetal brain and can influence the future neurological development of an infant. Up until the present, there is no method for the early detection of permanent consequences produced by fetal asphyxia. An objective way to determine the degree of asphyxia is the assessment of umbilical artery pH. This thesis studied the spontaneous motor behaviour of neonates within a wide range of umbilical artery pH.

Available data on the relationship between perinatal acidosis (low pH) and neurological development is scarce. Hopkins and Prechtl introduced the idea of observing spontaneous motor behaviour as a method for an early evaluation of the integrity of the brain.[58]

The observation of early spontaneous motor behaviour requires that a newborn shows spontaneous movements, is not sedated nor in need of assisted ventilation or parenteral fluids. These requirements yielded a group of infants born after an asphyctic episode, represented by a low umbilical artery pH without gross abnormal neurological symptoms or multiorgan failure.

Studying neonatal behaviour is only possible when the treatment for an asphyctic episode is no longer required. The aim of this thesis was to study whether the assessment of spontaneous motor behaviour could provide prognostic information for the management team and the parents on the future neurological development of the infant. Also, this method could provide indications for early physiotherapy.

Hopkins and Prechtl introduced the qualitative assessment of spontaneous motor behaviour as an early method to evaluate the integrity of the central nervous system in neonates by studying their general movements.[58] These authors, and others,[29,35,101] assessed some general movements of infants applying gestalt perception, classifying them as normal or abnormal. This qualitative assessment is reached by scoring the fluency, complexity and variability of a movement. According to these authors, the performance of a general movement is age-dependent and can be divided into the following types: 'preterm', 'term', 'writhing' and 'fidgety'. The individual development of general movements, especially the absence or presence of 'fidgety' movements at around 9 to 12 weeks after birth, is relevant to prognosis. One of these studies showed that repeated gestalt perceptions of asphyctic neonates with moderate or severe post-hypoxic encephalopathy is valuable for neurodevelopmental prognosis.[101]

Although gestalt perception yields more information than the study of the total of isolated items, changes in quality of the isolated items of general movements could still remain undetected due to the multiplicity of visual information achieved by gestalt observation. Therefore, slight brain dysfunctions could go undetected by the observer's eye. Because of this, we chose to score the quality of spontaneous motor behaviour by observing the isolated items of a general movement (van Kranen-Mastenbroek et al.).
In our study, all general movements per observation session were analysed. The combination of item scores of a general movement formed a movement type. The frequency of occurrence of any movement type per infant was calculated as a percentage of all general movements per observation session. Movement types occurring with a substantial frequency and those which could be relevant to each study group were selected. This allowed the study of spontaneous motor behaviour in infants with different conditions.
In this thesis, only full-term infants appropriate for gestational age, born in vertex position after an uncomplicated pregnancy were included. We studied 3 pH subgroups: pH <7.10 (acidosis), pH ≥7.10 and <7.20 and pH ≥7.20 in relation to spontaneous motor behaviour and neurological development.
At 18 months of age, there was a weak relationship between pH and abnormal neurological findings. Bayley scales showed normal scores, irrespective of pH, and abnormal neurological examinations were exclusively found in acidotic infants. However, 2 infants with an abnormal neurological examination showed low developmental indexes for both Bayley scales. Furthermore, another infant with an evident abnormal neurological examination showed normal scores at both Bayley scales. In conclusion, low pH at birth has no predictive value for neurological abnormal findings at 18 months of age.
The movement types in our study group evaluated in relation to pH, neurological examination and developmental scales at 18 months of age were characterised by 5 items of general movements: *onset of movement, speed, speed of arms compared to legs, amplitude of arms compared to legs* and *fluency.*
At 37-43 weeks postmenstrual age, the general movements of infants with an abnormal neurological examination and those of infants with low umbilical artery pH were more tremulous than those of other infants. However, 12 weeks later, no clear cut differences in general movements were observed in relation to pH. In infants with normal pH, general movements changed from fluent to jerky. In infants with low pH, general movements changed from tremulous to jerky. Irrespective of pH, the frequency of occurrence of the developmental items *pelvic tilting* and *hands to midline* increased with age in neurologically normal infants. No developmental trend was observed in neurologically abnormal infants. In acidotic neurologically

abnormal children, acidosis modified spontaneous motor behaviour and transient, tremulous movement types and a delay in the development of the pelvic tilting and bringing hands to midline was observed. However, all these changes had no prognostic significance for neurodevelopment at 18 months of age. The individual data of all infants showed a large variability with respect to the occurrence of movement types. Therefore, no characteristic movement types could be found with age (no clear cut developmental aspect) related to pH or neurodevelopmental outcome at 18 months of age. In conclusion, qualitative assessment of spontaneous motor behaviour was not predictive regarding neurological abnormal development.
Comparison between our results, based on our observation of spontaneous motor behaviour, and those of earlier studies using the gestalt method (Hopkins and Prechtl) is difficult. In our study, the observation of spontaneous motor behaviour showed no predictive value for abnormal neurological behaviour at 18 months of age. In contrast, Prechtl et al.[103] showed that observing the quality of spontaneous motor activity was valuable to predict neurological outcome in asphyctic full-term infants at 1.5, 2 years of age. In both studies asphyctic infants showed tremulousness; however, its predictive value was different. This difference could probably be explained by the fact that our population suffered less severe asphyxia and therefore, less brain damage. In contrast to Prechtl et al., we found tremulous movement types as the only abnormal finding. From our results, it can be concluded that in acidotic neonates the presence of spontaneous motor behaviour predicts normal neurological development.
The selection method for movement types used in this thesis can be applied in the same manner by other investigators to any study group. It is possible that brain dysfunctions due to subtle fetal brain damage could be detected by a qualitative scoring of individual items of general movements. However, because these dysfunctions might express themselves only with development, when new cortical functions are required, further evaluation of the relationship between spontaneous motor behaviour, pH and neurological outcome at 5 to 6 years of age is necessary. It would also be interesting to consider the quality of spontaneous motor behaviour in severe asphyctic neonates when they show spontaneous motility and medical support is no longer needed.

It can be concluded that the presence of spontaneous motor behaviour in acidotic infants is a favourable prognostic sign for neurodevelopment at 1.5 years of age. Regarding the qualitative assessment of movements, no predictive factors related to neurodevelopmental abnormal findings were found. ■

Samenvatting en conclusies

Ischemie en hypoxie (asfyxie) van de foetus voor de geboorte bedreigen de hersenen en kunnen hierdoor van invloed zijn op de neurologische ontwikkeling van het kind. Een manier om vroegtijdig blijvende gevolgen van asfyxie vast te stellen, ontbreekt. Een objectieve methode om de ernst van asfyxie te bepalen, is het meten van de zuurgraad (pH) in het bloed van de navelstrengarterie direct na de geboorte. In dit onderzoek worden pasgeborenen bestudeerd die onderling een grote variatie in pH vertonen.
De correlatie tussen acidosis (lage pH) en neurologische ontwikkeling is gering. Hopkins en Prechtl introduceerden observatie van spontaan motorisch gedrag als een manier om vroegtijdig het geïntegreerd functioneren van het centrale zenuwstelsel te beoordelen.[58] In onze onderzoeksgroep bestudeerden wij of kwaliteit van motorisch gedrag het neurologisch functioneren voorspelt.
De vroegtijdige observatie van spontaan motorisch gedrag vereist aanwezigheid van motoriek en afwezigheid van beademing, sedatie en infusen. Op grond hiervan blijkt motorisch gedrag een onbruikbaar meetinstrument voor asfyctische pasgeborenen die niet bewegen en/of medische ondersteuning behoeven die op het gedrag van invloed is. Dit heeft geleid tot een onderzoeksgroep waarin de acidotische kinderen geen of over het algemeen weinig directe neurologische symptomen vertonen onder gelijktijdige afwezigheid van meervoudig orgaanfalen.
Bestudering van neonataal gedrag is pas mogelijk in een tijdsperiode waarin de mogelijkheid tot acute behandeling van asfyxie reeds is gepasseerd. Observatie van spontaan motorisch gedrag in onze onderzoeksgroep is dan ook niet bedoeld als een selectiemethode voor pasgeborenen die acute behandeling vereisen. De doelstelling van dit onderzoek is of beoordeling van spontaan motorisch gedrag van prognostisch belang is voor de neurologische ontwikkeling van het kind. Het observeren van spontane motoriek kan een methode zijn om, indien geïndiceerd, tijdig fysiotherapeutische behandeling te starten.
Concluderend is het van belang om spontaan motorisch gedrag te bestuderen in relatie tot de pH in het arteriële navelstrengbloed en de neurologische ontwikkeling.

Hopkins en Prechtl introduceerden bestudering van spontaan motorisch gedrag van de pasgeborene, dat wil zeggen observatie van lichaamsbewegingen waarbij het hele lichaam betrokken is (grote lichaamsbewegingen), als methode om het geïntegreerd functioneren van het centrale zenuwstelsel vroegtijdig te beoordelen.[38] Zij, en volgende onderzoekers,[29,35,101] achten de gestaltwaarneming van enkele grote lichaamsbewegingen van een kind met als totaaloordeel 'normaal' of 'abnormaal' het meest relevant. Dit oordeel is gebaseerd op het vloeiende, complexe en variabele verloop van een beweging. Naar hun oordeel blijkt de uitingsvorm van een grote lichaamsbeweging leeftijdsafhankelijk en te onderscheiden in 'preterme', 'à terme', 'writhing' en 'fidgety' bewegingen. Het ontwikkelingsverloop van deze grote lichaamsbewegingen, waaronder met name de af- of aanwezigheid van 'fidgety' bewegingen rond 9 tot 12 weken na de geboorte, is individueel gezien van prognostisch belang. Het is onder andere gebleken dat de evolutie van herhaalde gestaltpercepties in een groep asfyctische pasgeborenen met matige tot ernstige posthypoxische encefalopathie prognostische betekenis voor de neurologische ontwikkeling heeft.[103] Concluderend is volgens Prechtl e.a. de herhaalde gestaltobservatie in de individuele ontwikkeling van spontaan motorisch gedrag een geschikte prognostische parameter ten aanzien van de neurologische ontwikkeling in diverse studiegroepen.

Gestaltkwaliteit omvat meer dan de som der onderdelen alleen. Echter veranderingen in de afzonderlijke kwaliteiten van een grote lichaamsbeweging kunnen verborgen blijven door de veelheid aan visuele informatie. Zo kunnen discrete disfuncties van de hersenen aan het oog onttrokken worden. Omdat met name subtiele disfuncties door de gestaltwaarneming gemaskeerd kunnen blijven, kozen wij ervoor, evenals Van Kranen-Mastenbroek e.a., om spontaan motorisch gedrag te bestuderen gebaseerd op beoordeling van afzonderlijke kwaliteitsaspecten van de grote lichaamsbeweging.

In dit onderzoek zijn alle grote lichaamsbewegingen die de kinderen gedurende de observatieperioden vertoonden, geanalyseerd. Door de beoordelingen van de diverse kwaliteitsaspecten van een grote lichaamsbeweging te combineren, wordt een beweging getypeerd. Het vóórkomen van ieder bewegingstype wordt voor elk kind in een percentage van alle, in die observatieperiode uitgevoerde grote lichaamsbewegingen, uitgedrukt. De vaker vóórkomende en zich onderscheidende bewegingstypen kunnen voor iedere onderzoeksgroep worden geselecteerd door middel van statistische methoden. Het spontaan motorisch gedrag van kinderen met diverse hersenaandoeningen kan op deze manier worden bestudeerd.

In de door ons beschouwde onderzoeksgroep worden kinderen bestudeerd met een grote variatie in de pH van de arteriële navelstreng, gemeten direct na de geboorte. Het betreft uitsluitend kinderen met een normaal geboortegewicht, geboren in hoofdligging, geboren na een voldragen, ongecompliceerde zwangerschap. Door het ontbreken van spontane motoriek in de eerste levensweek en/of door de noodzaak van medische ondersteuning die het spontane gedrag kan beïnvloeden, vielen klinisch ernstig asfyctische kinderen buiten onze onderzoeksgroep. Deze studie betreft pasgeborenen met een grote onderlinge variatie in pH. Wij hebben de pH gekozen als objectieve maat voor asfyxie. Wij bestudeerden 3 pH-intervallen: pH <7.10 (acidosis), pH ≥7.10 en pH <7.20, pH ≥7.20 in relatie tot neurologische ontwikkeling en spontane motoriek. Er bestaat geen eenduidige relatie tussen pH en een afwijkende neurologische ontwikkeling bij de leeftijd van 18 maanden. Beide Bayley's ontwikkelingsschalen tonen scores binnen de norm, onafhankelijk van pH. Daarentegen worden afwijkende neurologische onderzoeken uitsluitend bij acidotische kinderen gezien. Echter, slechts 2 kinderen met een afwijkend neurologisch onderzoek tonen eveneens afwijkende testresultaten voor beide ontwikkelingsschalen. Bovendien had 1 van de 2 kinderen met een evident abnormaal neurologisch onderzoek normale ontwikkelingsscores. Concluderend heeft een lage pH bij de geboorte geen voorspellende waarde voor een neurologisch afwijkende ontwikkeling bij de leeftijd van 1,5 jaar.
Bewegingstypen in deze studiegroep, bestudeerd in relatie tot pH, neurologisch onderzoek en ontwikkelingsschalen bij 18 maanden, worden gekenmerkt door 5 bewegingsmodaliteiten. Het betreft de items: *start van de beweging, snelheid, snelheid van armen ten opzichte van benen, amplitude van armen ten opzichte van benen* en *bewegingsverloop*.
In de eerste levensweek onderscheiden zowel neurologisch afwijkende kinderen als acidotische kinderen zich van de andere groepen door het vaker vóórkomen van bewegingstypen met een trillend bewegingsverloop. Echter, rond de leeftijd van 3 maanden is dit verschil in kwaliteit van grote lichaamsbewegingen verdwenen en niet meer aan pH gerelateerd. Zowel de trillerige bewegingstypen die vaker vóórkomen bij kinderen met een lage pH als de vloeiende bewegingstypen die meer vertoond worden door kinderen met een normale pH, ontwikkelen zich tot schokkerig verlopende bewegingstypen.
Neurologisch normale kinderen vertonen, onafhankelijk van de pH, bij de leeftijd van 3 maanden progressie in het optreden van beide ontwikkelingsparameters: *bekkenkanteling* en *het brengen van beide handen naar het midden*. Deze progressie wordt niet gezien bij de neurologisch abnormale, acidotische kinderen.

Acidosis beïnvloedt spontaan motorisch gedrag, zich uitend in voorbijgaande, vaak trillend verlopende bewegingstypen; het achterblijven van bekkenkanteling en het achterblijven van het brengen van beide handen naar het midden bij kinderen met een abnormaal neurologisch onderzoek. Dit afwijkend spontaan motorisch gedrag heeft geen prognostische betekenis voor de neurologische ontwikkeling bij de leeftijd van 1,5 jaar. Bij de meeste kinderen is er gedurende alle observaties een grote variatie in het aantal vóórkomende bewegingstypen. Er bestaat geen eenduidige relatie tussen bewegingstypen c.q. ontwikkeling van bewegingstypen, pH, neurologische of ontwikkelingsparameters bij de leeftijd van 1,5 jaar. Concluderend hebben de kwalitatieve aspecten van spontaan motorisch gedrag geen voorspellende waarde voor een neurologisch abnormale ontwikkeling.

Een reële vergelijking tussen de resultaten gevonden bij observatie van spontaan motorisch gedrag gerelateerd aan neurologische ontwikkeling gebaseerd op de observatie-methode volgens Hopkins en Prechtl in de reeds verrichte studies enerzijds, en de huidige studie anderzijds, is niet goed mogelijk. In de huidige studiegroep kan aan observatie van spontaan motorisch gedrag geen voorspellende waarde worden toegekend voor abnormaal neurologisch gedrag bij de leeftijd van 18 maanden. Dit is in tegenspraak met de gedragsobservaties van Prechtl e.a.[103] in asfyctische à terme kinderen die wel prognostische waarde met betrekking tot de neurologische ontwikkeling bij de leeftijd van 1,5 tot 2 jaar vonden. In beide studiegroepen tonen asfyctische kinderen trillerigheid; de voorspellende waarde hiervan is tegengesteld. Dit verschil in predictieve waarde van spontane motoriek is waarschijnlijk terug te voeren op een minder ernstige hersenbeschadiging in onze studiegroep. Onze gedragsobservaties laten immers, in tegenstelling tot Prechtl e.a., ondanks gedetailleerde bestudering, uitsluitend trillend verlopende bewegingstypen als afwijkende bevinding zien.

Wel kan uit onze resultaten worden geconcludeerd dat de aanwezigheid van spontaan motorisch gedrag in acidotische kinderen voorspellend is voor een normale neurologische ontwikkeling.

Van groot belang is dat het selecteren van bewegingstypen op basis van de hier beschreven methode door derden in iedere studiegroep op identieke wijze kan worden toegepast. Door het observeren van afzonderlijke kwaliteitsaspecten is het wellicht mogelijk disfuncties van de hersenen als gevolg van discrete foetale hersenbeschadiging op te sporen. Deze mogelijke disfuncties zullen aan het licht komen naarmate er gedurende de ontwikkeling meer aanspraak gemaakt gaat worden op de hogere corticale functies. Nadere evaluatie van de relatie tussen spontaan motorisch gedrag, pH en neurologische ontwikkeling op 5 à 6 jarige

leeftijd is in de toekomst vereist. Naast onderzoek naar deze relatie is het interessant de kwaliteit van spontaan motorisch gedrag te bestuderen van kinderen die ernstiger asfyctisch zijn dan de door ons bestudeerde onderzoeksgroep. Observatie is dan mogelijk vanaf het moment dat de kinderen spontaan motorisch gedrag gaan vertonen en ondersteunende medische behandeling niet langer noodzakelijk is.

Geconcludeerd kan worden dat het vertonen van spontaan motorisch gedrag door acidotische kinderen prognostisch gunstig is voor de neurologische ontwikkeling bij de leeftijd van 1,5 jaar. Echter in de kwaliteit van de motoriek zijn geen factoren gevonden die een neurologisch abnormale ontwikkeling voorspellen. ■

Appendices

Table 1

Complicated pregnancy; adapted from Kloosterman.[61]

1. Diseases influencing or influenced by pregnancy:
   - neurological diseases: epilepsy, subarachnoidal haemorrhage, multiple sclerosis, brain tumour, psychiatric disorders;
   - internal diseases: active tuberculosis, severe chronic obstructive pulmonary disease (COPD), cardiovascular diseases, morbus Addison, hypo- and hyperthyroidism, thrombosis and embolism;
   - essential hypertension, diabetes mellitus, renal disease, active rhesus antagonism.

2. Obstetrical complications:
   - pregnancy-induced hypertension, defined as a condition with blood pressure higher than 150/95 or diastolic persistent 90, measured on 2 independent occasions;
   - preeclampsia defined as pregnancy-induced hypertension complicated by proteinuria of at least 100 mg/24 hours;
   - eclampsia;
   - haemolysis, elevated liver function tests, low platelet counts (HELLP) syndrome;
   - pregnancy-induced diabetes mellitus;
   - severe vaginal blood loss during pregnancy;
   - hyperemesis gravidarum with acetonuria;
   - adnex tumour requiring treatment;
   - prolonged ruptured membranes (>24 hours);
   - clinically significant hydramnion;
   - pyelitis;
   - fetal abnormalities, demonstrated or suspected by antenatal diagnostics;
   - rhesus sensibilisation;
   - laparotomy after the 26th week.

Table 2 *Items and their possible scores used in the quality score of general movements.*[68,69]

	item	scores
1.	Onset of movement	0=abrupt/1=smooth
2.	Variability in speed	0=absent/1=present
3.	Overall speed	0=predominantly fast 1=predominantly slow
4.	Speed of arms compared to legs	0=higher/1=lower/2=equal
5.	Force against gravity	0=absent/1=present
6.	Variability in amplitude	0=absent/1=present
7.	Overall amplitude	0=predominantly large 1=predominantly small
8.	Amplitude of arms compared to legs	0=larger/1=smaller/2=equal
9.	Fluency	0=not fluent-tremulous 1=not fluent-flapping 2=not fluent-abrupt/jerky 3=fluent

(cont')

	item	scores
10.	Overall variability	0=absent/1=present
11.	Variability in arms	0=absent/1=present
12.	Variability in legs	0=absent/1=present
13.	Head involvement	0=no/1=yes
14.	Trunk involvement	0=no/1=yes
15.	Left arm involvement	0=no/1=yes
16.	Right arm involvement	0=no/1=yes
17.	Left leg involvement	0=no/1=yes
18.	Right leg involvement	0=no/1=yes
19.	Fine distal movements	0=absent/1=present
20.	End of movement	0=abrupt/1=smooth
21.	Global assessment	0=abnormal/1=normal
22.	Pelvic tilting	0=absent/1=present
23.	Hands to midline	0=absent/1=present

Table 3

Explanation of terms used in the quality score of general movements.[68,69]
Several items are not mentioned since they do not need any further explanation.

1. *Onset of movement:*
the item is scored *smooth* if the movement has a gradual onset, beginning in one limb and spreading slowly to the other limbs, with a gradual increase in intensity. The item is scored *abrupt* if the movement begins with a sudden movement of one or more limbs and with a high intensity.

3. *Speed:*
the item is scored *predominantly fast* if most of the components of the movement have a high speed, and *predominantly slow* if most components have low speed. The observer must give his own interpretation concerning *high* and *low* speed.

4. *Speed of arms compared to legs:*
scored as *higher* if arms move faster than legs, *equal* if arms and legs have the same speed, *lower* if arms move more slowly than the legs.

7. *Amplitude:*
the amplitude of the general movement is scored *predominantly large* if most of the movements of arms and legs have a large amplitude, i.e. if the movements in respectively elbow and/or shoulder or knee and/or hip have an amplitude which is equal to or larger than 50% of the maximal amplitude. Otherwise the amplitude of the general movement is scored *predominantly small.*

8. *Amplitude of arms compared to legs:*
scored *equal, larger* or *smaller* if the movements of the arms have respectively the same, a larger or smaller amplitude than the movements of the legs.

9. *Fluency:*
the movement is scored *fluent* if it is continuous with gradual accelerations and decelerations, without tremulous components. The movement is scored *not fluent* if it is tremulous, flapping or abrupt and jerky with sudden accelerations and decelerations.[13]

(cont')

10-12. The items *overall variability* and *variability in arms and legs* are scored *present* if various patterns are present in the total general movement, in the movements of arms and in the movements of legs. Otherwise, items are scored *absent.*

21. *Global assessment:*
the quality of the general movement is assessed *normal* or *abnormal* according to the general impression and interpretation of the observer.

22. *Pelvic tilting:*
pelvic tilting is scored *present* if from a supine position hips abduct, externally rotate and flex ≥90% by active abdominal muscles accompanied by flexed knees. Otherwise pelvic tilting is scored *absent.*

23. *Hands to midline:*
the item is scored *present* if from a supine position with both shoulders abducted, both hands go to the midline by adduction of the shoulders. Otherwise, the item is scored *absent.* ■

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Twijfel is een eerbetoon aan de waarheid

(J.E. RENAN)

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